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(54) **Polysulfate of cyclodextrin derivative and process for preparing the same.**

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EP-A- 0 240 098
WO-A-90/00596
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Description

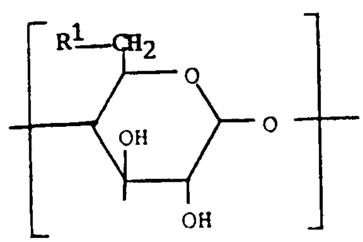
This invention relates to a novel polysulfate of a cyclodextrin derivative having antiretrovirus activity and processes for preparing the same.

AIDS (acquired immunodefficiency syndrome) is a lethal or extremely malignant disease which is caused by infection of human immunodefficiency virus (HIV) which is a kind of retroviruses. Prevention and destruction thereof are now most serious problem to be overcome by human being with world-wide scale.

As a compound having antiretrovirus activity, there have been known, for example, azidothimidine (IGAKUNOAYUMI (Walking of Medicine), Vol. 142, No. 9, pp. 619 to 622 (1987)), sulfated polysaccharides (Japanese Provisional Patent Publications No. 45223/1988 and No. 25724/1989), and the like.

In Patent WO-A-90/00596 there is described use of a cyclic oligosaccharide derivative having up to 12 sugar monomers characterised by a solubility at 0°C in distilled water of at least 20 gm/100 ml, as a blocking agent capable of interacting with the cells or virus. Cyclic oligosaccharides disclosed include an alpha, beta or gamma cyclodextrin.

Cyclodextrin derivatives are also referred to in US-A-3974274 which discloses a cyclodextrin derivative of the formula:



wherein R^1 is amino, methylamino or dimethylamino and n is an integar of 6 and 7.

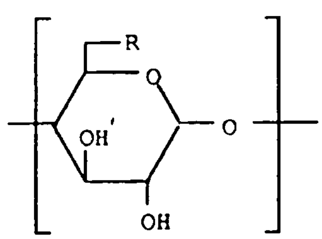
However, it has not yet fully been made clear or confirmed whether or not conventionally known chemicals having an antiretrovirus activity are effective for and safe to the therapy of AIDS.

An object of the present invention is to provide a novel compound having an excellent antiretrovirus activity, particularly an excellent proliferation-inhibiting activity against HIV.

Another object of the present invention is to provide a process for preparing the novel compound.

A further object of the present invention is to provide intermediate compounds for preparing the novel compound.

The present invention relates to a polysulfate of a cyclodextrin and a process for preparing the same in which at least one of 6 to 8 D-glucose units constituting the cyclodextrin has been replaced by a unit represented by Formula(I):



(I)

wherein R is a group represented by the formula: 1) $-OSO_2R^1$, 2) $-SR^2$,

$$3)\ -\overset{\displaystyle R^3}{\overset{|}{N}}R^4,$$

4) $-NHSO_2R^5$ or

5) $-\overset{R^7}{\overset{|}{N}}COR^6$;

where R^1 represents a mesityl group;

R^2 represents an C_{1-20} alkyl group; a C_{1-4} alkyl group having 1 to 3 substituents selected from phenyl, a halogeno-substituted phenyl group and a C_{1-4} alkoxy-substituted phenyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a dihydroxy-substituted pyrimidinyl group or a purinyl group,

one of R^3 and R^4 represents a C_{1-4} alkyl group;

a hydroxy-substituted C_{1-4} alkyl group; an amino-substituted C_{1-4} alkyl group; a C_{3-8} cyloalkyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a C_{1-4} alkoxy phenyl-substituted C_{1-4} alkyl group; a phenyl-substituted C_{1-4} alkyl group; and the other represents a hydrogen atom or a C_{1-4} alkyl group, or both may be combined at their ends to form a C_{1-4} alkylene group,

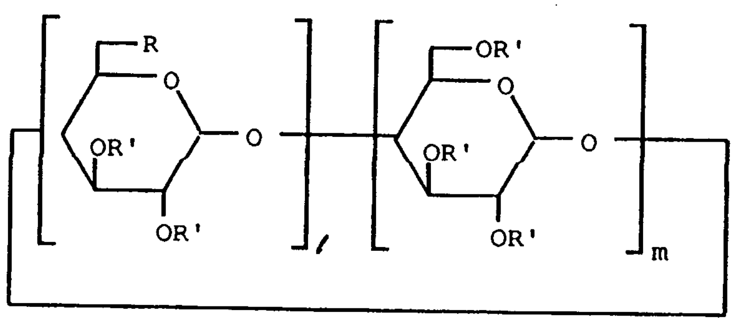
R^5 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a naphthyl group; a thienyl group; a C_{1-4} alkyl-substituted isooxazolyl group or a C_{1-4} alkyl-substituted thiazolyl group;

R^6 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from a hydroxy group, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a phenyl-substituted C_{1-4} alkyl group; a thienyl group; or a pyrenylcarbonyl-substituted C_{1-4} alkyl group; and

R^7 represents a hydrogen atom; or a C_{1-4} alkyl group substituted by a C_{2-5} alkanoylamino group or a benzoylamino group, or a salt thereof.

A process for preparing the above-defined polysulfate compound according to the present invention comprises reacting a cyclodextrin derivative in which at least one of 6 to 8 D-glucose units constituting the cylclodextrin is replaced by the unit or units represented by the above Formula(I), with a sulfonating agent, and then converting the product into a salt, if desired.

The polysulfate compound of the present invention may be represented more specifically as follows:



(II)

wherein R is of the same meaning as in Formula(I); at least one of R's represents a SO_3H group and the other R's represent a hydrogen atom. Further, ℓ + m equals 6, 7 or 8. When the sum, ℓ + m equals 6, the polysulfate compound is a derivative of α-cyclodextrin. When the sum, ℓ + m equals 7, it is a derivative of β-cyclodextrin. When the sum ℓ + m equals 8, it is a derivative of γ-dextrin.

It should be understood that constructional glucose and substituted glucose unit(s) (I) are forming a cyclic ring in an arbitrary order through linkage between the 1-position and the 4-position.

The term "alkyl" in this specification means straight-chain or branched alkyl having 1 to 20 carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, heptyl, octyl, nonyl and octadecyl.

The term "lower-alkyl" means straight-chain or branched alkyl having 1 to 4 carbon atoms such as methyl, ethyl, propyl and butyl.

The term "lower alkoxy" means alkoxy having 1 to 4 carbon atoms such as methoxy, ethoxyl, propoxy and butoxy.

The term "lower alkanoyl" means alkanoyl having 2 to 5 carbon atoms such as acetyl, propionyl, butyryl and valeryl.

The lower alkyl group having 1 to 3 substituted or unsubstituted phenyl groups, represented by R^2, includes a benzyl group, a trityl group, a phenethyl group, a chlorobenzyl group and a methoxybenzyl group.

The substituted or unsubstituted phenyl group, represented by $R^{2,}$ includes a phenyl group, a chlorophenyl group, a methylphenyl group and a methoxyphenyl group.

The nitrogen-containing heterocyclic group which may have a substituent(s), represented by R^2, includes a dihydroxypyrimidinyl group and a purinyl group.

The hydroxy-substituted lower alkyl group reprsented by R^3 or R^4 includes a hydroxyethyl and a dihydroxypropyl group.

The amino-subsututited lower alkyl group, represented by R^3 or $R^{4,}$ includes an aminoethyl group.

The cycloalkyl group represented by R^3 or R^4 includes a cycloalkyl group having 3 to 8 carbon atoms such as a cyclohexyl group.

The lower substituted or unsubstituted phenyl group represented by R^3 or R4 includes a chlorophenyl group, a methylphenyl group, a methoxyphenyl group and an ethoxyphenyl group. The substituted or unsubstituted phenyl-substituted lower alkyl group represented by one of R^3 and R^4 includes a benzyl group, a methoxybenzyl group and a phenethyl group.

The lower alkylene group formed by a combination of R^3 and R^4 includes a butylene group and a pentamethylene group.

The substituted or unsubstituted phenyl group, represented by R^5, includes a phenyl group, a methylphenyl group, a methoxyphenyl group and a chlorophenyl group.

The heterocyclic group which may have substituents(s), represented by $R^{5,}$ includes a furyl group, a thienyl group, an oxazolyl group, an isooxazolyl group, a thiazolyl group, an isothiazolyl group, a dimethylisooxazolyl group and a dimethylthiazolyl group. The sulfur-containing heterocyclic group represented by R^6 includes a thienyl group.

The substituted or unsubstituted phenyl group, represented by $R^{6,}$ includes a phenyl group, a hydroxyphenyl group, a methylphenyl group and a methoxyphenyl group.

The phenyl-substituted lower alkyl group, represented by $R^{6,}$ includes a benzyl group.

The pyrenylcarbonyl-substituted lower alkyl group, represented by $R^{6,}$ includes a pyrenylcarbonylethyl group.

The lower alkyl group substituted by a lower alkanoylamino group or a benzoylamino group, represented by R^7, includes a lower alkyl group substituted by an acetylamino group, a propionylamio group or a benzoylamino group.

Of the polysufate derivative of a cyclodextrin where R represents a group $-OSO_2R^1$, a polysulfate compound having 8 to 23 sulfate groups in the molecule is preferred.

Of the polysulfated derivative where R represents a group $-SR^2$, a polysulfate compound having 8 to 23 sulfate groups in the molecule is preferred, and there may be mentioned, as preferable compounds, a polysulfate compound where R^2 represents a C_{1-20} alkyl group; a C_{1-4} alkyl having 1 to 3 substituents selected from a phenyl group, a halogeno-substituted phenyl group and C_{1-4} alkoxy-substituted phenyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a dihydroxy-substituted pyrimidinyl group or purinyl group,

Of the polysulfate derivative where R represents a group

$$\begin{array}{l} R^3 \\ | \\ -N-R^4, \end{array}$$

a polysulfate compound having 8 to 23 sulfate groups in the molecule is preferred, and there may be mentioned, as preferable compounds, a polysulfate compound where one of R^3 and R^4 represents a C_{1-4} alkyl group; a hydroxy-substituted C_{1-4} alkyl group; an amino-substituted C_{1-4} alkyl group; a c_{3-8} cycloalkyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a phenyl-substituted C_{1-4} alkyl group; a C_{1-4} alkoxyphenyl-substituted C_{1-4} alkyl group; and the other is a hydrogen atom or a C_{1-4} alkyl group;
or both is combined at their ends to form a C_{1-4} alkylene group.

Of the polysulfate derivative where R represents a group, $-NHSO_2R^5$, a polysulfate compound having 8 to 23 sulfate groups in the molecule is preferred, and there may be mentioned, as preferred compounds, a polysulfate compound where R^5 represents a C_{1-20} alkyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a naphthyl

group; a thienyl group; a C_{1-4} alkyl-substituted isooxazolyl group or a C_{1-4} alkyl-substituted thiazolyl group.

Of the polysulfate derivative where R represents a group

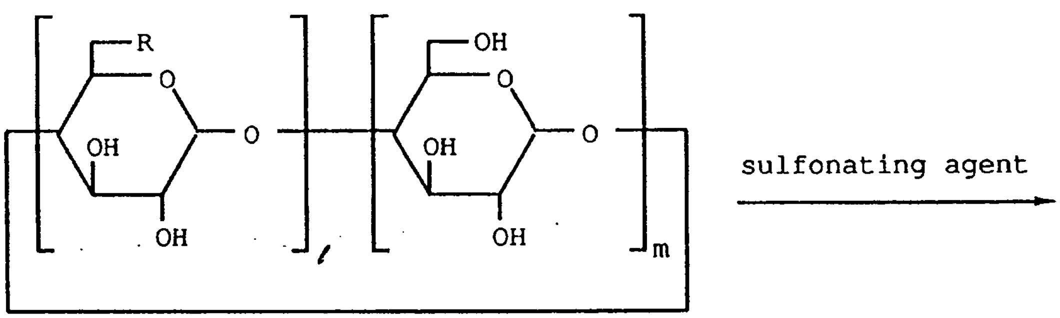
$$\begin{array}{l}\;\;R^7\\ \;\;|\\ -NCOR^6,\end{array}$$

a polysulfate compound having 8 to 23 sulfate groups in the molecule is preferred, and there may be mentioned, as preferable compounds, a polysulfate compound where R^6 represents a straight-chain or branched C_{1-20} alkyl group; a phenyl group; a hydroxy-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a phenyl-substituted C_{1-4} alkyl group; a thienyl group or a pyrenylcarbonyl-substituted C_{1-4} alkyl group and R^7 is a hydrogen atom; a C_{2-5} alkanoylamino-substituted C_{1-4} alkyl group or a benzoylamino-substituted C_{1-4} alkyl group.

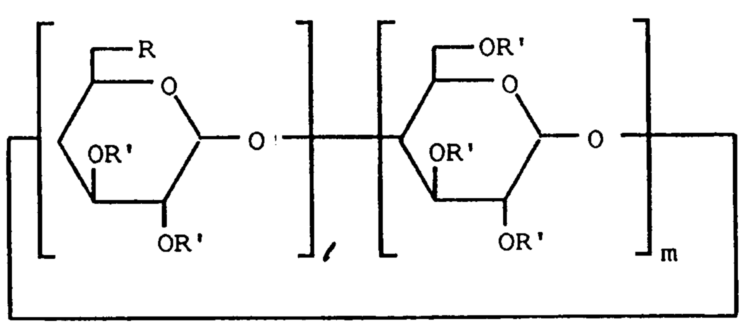
More preferred examples of the compound of the invention are those of Formula (II) wherein R is a N-benzoyl-N-2-benzoylaminoethylamino group, an octadecanoylamino group, a hexanoylamino group, an octanoylamino group, a 1-pyrenylcarbonylpropanoylamino group, a 4-metoxyphenylamino group, a 2-naphthylsulfonyloxy group, an octylsulfonylamino group, a mesitylenesulfonyloxy group, a benzylthio group, a 4-chlorobenzylthio group, a 4-methoxybenzylthio group, a 4-methylphenylthio group, a 4-methoxyphenyl group or a purinylthio group.

The polysulfate compound according to the present invention may be prepared by reacting a cyclodextrin derivative in which at least one of 6 to 8 D-glucose units constituting the cyclodextrin is replaced by the unit or units represented by the above Formula(I), with a sulfonating agent, and then converting the product into a salt, if desired.

The reaction may be illustrated as follows:



(III)



(II)

(wherein R, R', ℓ, and m have the same meanings as defined above)

The reaction of Compound(III) with the sulfonating agent may be carried out in a suitable solvent.

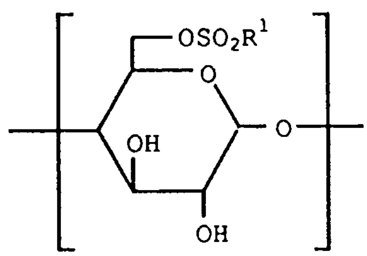
As the sulfonating agent, there may suitably be used, for example, a sulfur trioxide complex such as sulfur trioxide-pyridine complex, sulfur trioxide-trialkylamine complex, sulfur trioxide-dioxane complex, sulfur trioxide-dimethylformamide complex and the like; anhydrous sulfuric acid; concentrated sulfuric acid; chlorosulfonic acid; and so on.

The amount of the sulfonating agent to be used may preferably be in excess of the amount of the starting compound(III). For example, in cases where sulfur trioxide-pyridine complex or sulfur trioxide-trialkylamine complex is used as the sulfonating agent, the amount thereof to be used may preferably be 1 to 10 equivalents, especially 2 to 5 equivalents relative to the amount of Compound(III).

As the solvent for reaction, there may preferably be used, for example, a tertiary amine such as pyridine, picoline, lutidine, N,N-dimethylformamide, formamide, hexamethylenephosphoryltriamide, chloroform, benzene, toluene, xylene, water, a mixture of these solvents, liquid sulfur dioxide and so on.

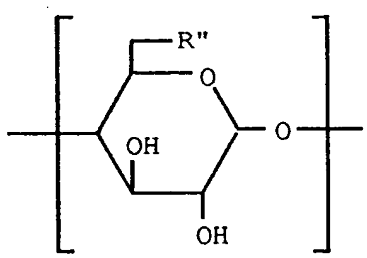
The reaction can be carried out under cooling to under heating and may preferably be carried out under heating.

In the above-mentioned reaction, when a β-cyclodextrin in which R is a $-OSO_2R^1$ is used as the starting compound (III) and sulfur trioxde-pyridine or sulfur trioxide-trialkylamine complex is used as the sulfonating agent, there can be obtained a sulfate of a β-cyclodextrin in which one to 7 D-glucose units constituting β-cyclodextrin has been replaced by a unit represented by Formula (IV)



(IV)

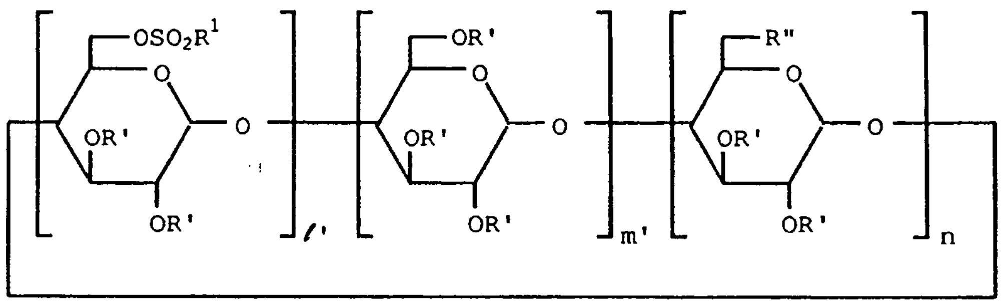
where R^1 is the same as defined above, and 0 to 2 D-glucose units has been replaced by a unit represented by Formula (V)



(V)

wherein R" is a pyridinio group or a lower-alkylamino group.

The above-mentioned polysulfate compound may be represented more specifically as follows;



(VI)

wherein R^1 is of the same meaning as in formula (I); at least one of R's represents a SO_3H group and the other R's represent a hydrogen atom; and R" represents a pyridinio group or a lower-alkylammonio group. Further, ℓ' + m' + n equals 7. ℓ' is an integer of 1 to 7; m' is an iteger of 0 to 6 more accurately 0 to (ℓ' + m' + n - 1); n is an integer of 0 to 2.

More specifically, the product is obtained as a mixture of the compounds in which n is O, 1, or 2 in Formula (VI) by selecting optionally the reaction conditions. For example, when the reaction is carried out at a temperature of 40 to 70 °C, the compound in which n is 0 is the main product, and when the reaction is carried out at a temperature of 70 to 110 °C, the compound in which n is 1 or 2 can be produced as the main product.

In the latter case, in cases where the sulfonating is sulfur trioxide-pyridine complex, a compound in which R^1 is a pyridinio group may be obtained, and in cases where it is sulfur trioxide-trialkylamine complex, a compound in which R^1 is a trialkylammonio group may be obtained.

After completion of the reaction, the desired reaction product can be isolated and purified. For example, the crude product obtained from the reaction mixture is treated with an alkali metal hydroxide, followed by being passed through a column packed with a cross-linked dextran gel etc. to give the desired product as an alkali metal salt thereof.

The polysulfate compound according to the present invention may be used either in a free form or in the of a pharmaceutically acceptable salt thereof. As such salts, there may be mentioned, for example, an alkali metal salt such as a sodium salt, a potassium salt and a lithium salt; an alkaline earth metal salt such as a calcium salt, a magnesium salt and a barium salt; an organic amine salt such as a trimethylamine salt, a trietylamine salt, a pyridine salt, a glycine ethyl ester salt, an ethanolamine salt and a basic amino acid salt; and so on.

The polysulfate compound or a salt thereof according to the present invention may be administered either orally or parenterally(e.g., intravenous, intramuscular topical and subcutaneous administrations), and may be used in an ordinary manner, e.g., as an optional pharmaceutical preparation such as a tablet, a granule, a capsule, a powder and an injectable preparation.

The dosage amount of the compound according to the present invention to be administered as an active ingredient is different depending upon the age, body weight, conditions and the kind of symptoms of a patient and may suitably be around 0.1 to 500 mg/kg, preferably around 0.1 to 50mg/kg.

The starting compound(III) is a novel compound which can be prepared as follows. Namely, in cases where R is a $-OSO_2R^1$ group, the starting compound(III) can be obtained by subjecting a cyclodextrin to reaction with mesitylenesulfonyl chloride in a suitable solvent(e.g., pyridine) followed by isolation and purification in a conventional manner such as column chromatography and the like. In case where R is a $-SR^2$ group, the starting compound, a cyclodextrin sulfide derivative represented by Formula (III) can be prepared by subjecting a compound (III) in which R is a mesitylenesulfonyl group or an iodine atom to reaction with a mercaptan compound of the Formula

R^2SH

In cases where R is a $-NHSO_2R^5$ group, the starting compound, a cyclodextrin sulfonamide derivative represented by Formula(III) can be prepared by subjecting a cyclodextrin to reaction with a substituted sulfonic acid halide(e.g., mesitylenesulfonyl chloride), optionally by reacting with ammonia after isolation and purification of the reaction product, followed by optional sulfonamidation of the product. Further, in

cases where R is a $-NR^7COR^6$, the starting compound, an acylaminocylodetrin derivative represented by Formula (III) can be obtained by subjecting a cyclodextrin to reaction with a substituted sulfonic acid halide-(e.g., mesitylenesulfonyl chloride and naphthylsufonyl chloride) and optionally after isolation and purification, reacting the product with ammonia or a loweralkylenediamine, followed by optional acylation of the resulting product.

The present invention will be explained in more detail by way of the following Examples, Referential Examples and Test Examples, which should not however be construed to limit the scope of the present invention.

Example 1

To 1.0 g of heptakis (6-O-mesitylenesulfonyl)-β-cyclodextrin was added 50 ml of pyridine, and 2.77 g of sulfur trioxide-pyridine complex was further added thereto. After reaction at 70 °C for 6 hours, the supernatant was removed and the residue was evaporated to dryness under reduced pressure. The obtained light brown powder was dissolved in 10 ml of a 30 % sodium acetate solution, followed by purification on a column packed with Sephadex G-10 (trade name, manufactured by Pharmacia AB) to give 1 g of sodium salt of heptakis(6-O-mesitylenesulfonyl)-β-cyclodextrin polysulfate as a white powder.

$$\mathrm{IR}\ \nu_{max}^{Nujol}\ cm^{-1}\ :$$

1240, 1190, 1050, 1000, 820

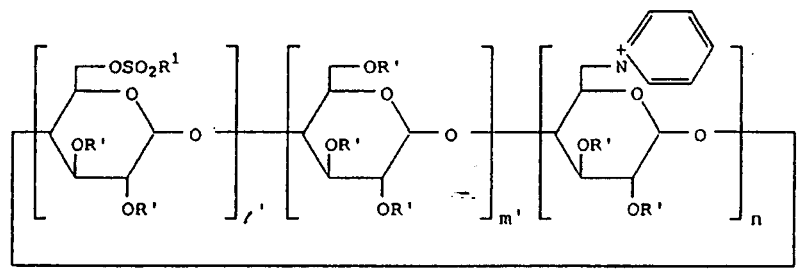
^{1}H-NMR(D_2O)δ : 2.25(brs), 2.45(brs), 6.9(brs)

The number of sulfate groups in the molecule to be calculated from the elementary analysis value: 10

Examples 2 to 4

An experiment was run in the same manner as in Example 1 except that mono(6-O-mesitylenesulfonyl)-β-cyclodextrin, bis(6-0-mesitylenesulfonyl)-β-cyclodextrin or tris(6-0-mesitylenesulfonyl)-β-cyclodextrin was reacted with sulfur trioxide-pyridine complex and that potassium acetate or potassium hydroxide was used in place of the sodium acetate to give the compound as shown in the following Table 1.

Table 1



(II)

[Provided that R^1 is a mesityl group.]

Example No.	Compound (VI)					Physical properties etc.			
	l'	m'	n	Number of sulfate group**	Kind of salt	Form	Yield (%)*	IR ν_{max}^{Nujol} cm^{-1}	^1H-NMR (D_2O) δ
2	1	6	0	20	K	Colorless powder	171	1240, 1120, 1000, 810	2.35(brs), 2.64(brs), 7.20(brs)
3	"	5	1	17	"	"	161	1240, 1440, 1000, 940, 810	2.35(brs), 2.64(brs), 7.20(brs), 8.15(brs), 8.4-9.2(m)
4	"	4	2	16	"	"	90	1240, 1040, 1000, 940, 810	2.35(brs), 2.60(brs), 7.20(brs), 8.15(brs), 8.5-9.3(m)

Note) *: Yield is shown in terms of % by weight relative to the starting compound.
**: The number of sulfate groups in the molecule to be calculated from the elementary analysis value.

Example 5

To 25 ml of pyridine, was added 0.4 g of heptakis(6-benzylthio-6-deoxy)-β-cyclodextrin and 1.42 g of sulfur trioxide-pyridine complex was further added thereto, followed by stirring at 70°C for 6 hours. After

the reaction mixture was allowed to stand for cooling, the supernatant was removed. After the residue was evaporated to dryness under reduced pressure and dissolved in 5 ml of water, the pH of the solution was adjusted to 8 with a 10% sodium hydroxide, followed by purification on a column packed with Sephadex G-10 (trade name, manufactured by Pharmacia AB) to give 0.22 g of sodium salt of heptakis(6-benzilthio-6-deoxy)-β-cyclodextrin polysulfate as a light yellow powder.

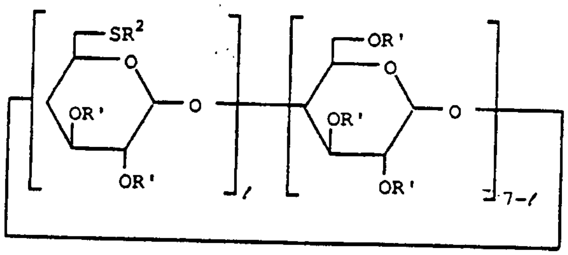
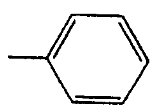
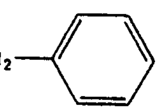
$$IR\ \nu_{max}^{Nujol} cm^{-1}:$$

1240, 1160, 1040, 830
^{1}H-NMR(D_2O)δ : 3.6(br,s), 6.8-7.4(br,s)
The number of sulfate groups in the molecule to be calculated from the elementary analysis value: 12

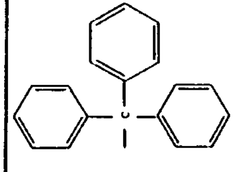
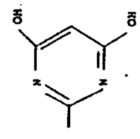
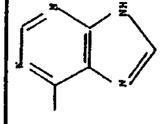
Examples 6 to 17

The corresponding starting compounds were treated in the same manner as in Example 1 to give the compounds as listed in the following Table 2.

Table 2

Example No.	 (II)							
	Compound (II)				Physical properties etc.			
	R^2	ℓ	Number of sulfate group***	Kind of salt	Form	Yield (%)*	IR ν_{max}^{Nujol} cm^{-1}	^1H-NMR (D_2O) δ
6		7	7	Na	Light brown powder	106	1240, 1040, 830	6.5-7.4 (br, s)
7	$-(CH_2)_4CH_3$	7	10	"	"	130	1240, 1040, 830	0.89 (br, t) ** 1.36 (br, s)
8	$-CH_2$ 	1	17	K	Colorless powder	178	1240, 1040, 810	7.2-7.3 (m)
9	"	2	16	"	"	203	1240, 1040, 810	7.3-7.7 (m)

(to be continued)

10	$-(CH_2)_4CH_3$	3	15	K	Colorless powder	221	1240, 1040, 1000, 820	7.1-7.6(m)
11	"	4	14	"	"	87	1240, 1040, 1000, 820	7.0-7.6(m)
12	"	5	14	"	"	72	1240, 1040, 1000, 820	7.0-7.6(m)
13	$-(CH_2)_{17}CH_3$	1	17	"	"	173	1240, 1000, 810	0.86(br,m), 1.28(br,m)
14		"	19	"	Light reddish brown powder	191	1240, 1040, 810	7.25(br,s)
15		"	19	"	Colorless powder	214	1240, 1040, 810	
16		"	17	"	"	164	1240, 1000, 940, 800	8.40(br,s) 8.70(br,s)
17	"	2	14	"	"	177	1240, 1040, 1000, 820	7.5-9.0(m)

Note) *: Yield is shown in terms of % by weight relative to the starting compound.

**: Values are at ^{1}H-NMR(DMSO-d_6)δ.

***: The number of sulfate groups in the molecule to be calculated from the elementary analysis value.

Example 18

To 1 g of heptakis(6-benzoylamino-6-deoxy)-β-cyclodextrin was added 75 ml of pyridine and 3.6 g of sulfur trioxide-pyridine complex was further added thereto. After reaction at 70°C for 6 hours, the supernatant was removed and the residue was treated with methanol and ethanol for pulverization. The

obtained powder was collected by filtration, dried and then dissolved in 5 ml of water. A 30% aqueous sodium acetate was added to the solution to give a sodium salt, followed by purification on a column packed with Sephadex G-10 (trade name, manufactured by Pharmacia AB) to give 0.87 g of sodium salt of heptakis(6-benzoylamino-6-deoxy)-β-cyclodextrin polysulfate as a light brown powder.

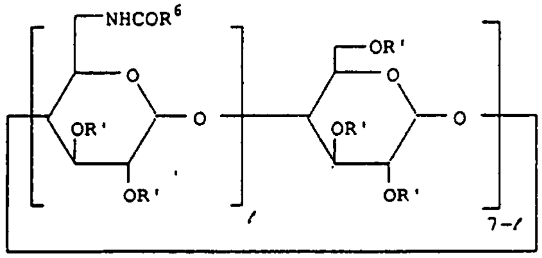
$$IR\ \nu_{max}^{Nujol} cm^{-1} \quad :$$

1640, 1600, 1240, 1040, 830
^{1}H-NMR(D_2O)δ : 7.1-7.5(br,s), 7.6-7.8(br,s)
The number of sulfate groups in the molecule to be calculated from the elementary analysis values: 12

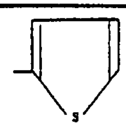
Examples 19 to 40

The corresponding compounds were treated in the same manner as in Example 18 to obtain the compounds as listed in the following Tables 3 and 4.

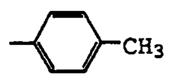
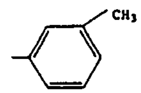
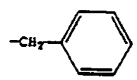
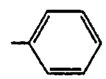
Table 3



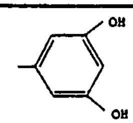
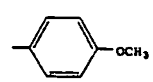
(II)

Example No.	Compound (II)				Physical properties etc.			
	R^6	ℓ	Number of sulfate group**	Salt	Form	Yield (%)*	IR ν_{max}^{Nujol} cm^{-1}	^{1}H-NMR (D_2O) δ
19	$-CH(CH_3)_2$	7	13	Na	Light brown powder	60	1650, 1540, 1240, 1040, 830	1.1(d)
20	$-(CH_2)_4CH_3$	"	"	"	White powder	69	1650, 1540, 1240, 1040, 830	0.82(br,t) 1.0-1.7(br,m), 2.0-2.3(br)
21	$-(CH_2)_5CH_3$	"	"	"	Light brown powder	120	1650, 1550, 1240, 1040, 820	0.88(br,s), 1.3(br,s), 1.6(br,s), 2.25(br,s)
22		"	9	"	"	103	1640, 1540, 1240, 1040, 830	6.5-7.8(br,m)

(to be continued)

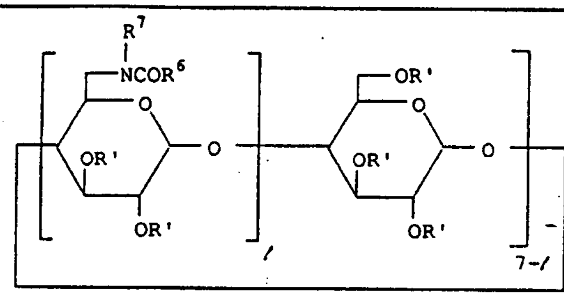
23		7	12	Na	White powder	60	1640, 1550, 1240, 1040, 840	1.6-2.3(br,m), 6.5-7.6(br,m)
24		"	"	"	Light brown powder	105	1650, 1600, 1540, 1240, 1040, 830	1.6-2.2(br), 6.4-7.0(br)
25		"	10	"	Brown powder	40	1650, 1600, 1540, 1500, 1240, 1040, 830	7.1(br)
26		1	17	K	White powder	223	1640, 1550, 1240, 1160, 1050, 1000, 940, 880, 810	7.4-7.7(br,s), 7.7-7.9(br,s)
27	$-(CH_2)_{16}CH_3$	"	"	"	"	219	1640, 1550, 1240, 1000, 950, 810, 740, 620, 580	0.85(t), 1.27(s), 1.5-1.7(m), 2.2-2.5(m)
28	$-(CH_2)_6CH_3$	"	16	"	"	236	1640, 1550, 1240, 1000, 810, 740, 620, 580	0.7-1.0(m), 1.30(br,s), 1.5-1.8(m), 2.2-2.5(m)
29	$-(CH_2)_4CH_3$	"	17	"	"	238	1640, 1550, 1240, 1000, 940, 880, 810, 740, 690, 580	0.8-1.0(m), 1.1-1.4(m), 1.5-1.8(m), 2.1-2.5(m)
30	$-(CH_2)_{16}CH_3$	2	18	"	"	206	1640, 1550, 1240, 1160, 1040, 1000, 950, 810, 740, 580	0.8-1.2(m), 1.29(br,s)

(to be continued)

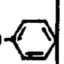
31	$-(CH_2)_{16}CH_3$	3.5 ***	17	K	Light brown powder	138	1640, 1550, 1240, 1160, 1040, 1000, 945, 810, 740, 580	0.85(t) 1.23(br,s)
32	$-(CH_2)_{16}CH_3$	"	15	"	White powder	186	1640, 1550, 1240, 1040, 1000, 820	0.87(br,s), 1.28(br,s), 1.4-1.7(m), 2.0-2.5(m)
33	$-(CH_2)_4CH_3$	"	16	"	"	74	1640, 1550, 1240, 1160, 1040, 1000, 950, 810, 740, 580	0.87(br,s), 1.30(br,s), 1.59(br,s), 2.29(br,s)
34		1	17	"	"	235	1640, 1550, 1240, 1160, 1000, 940, 810, 740, 580	7.1-7.6(m)
35		"	15	"	"	237	1640, 1510, 1240, 1000, 940, 880, 810, 740, 690, 620, 580	6.9-7.2(m), 7.7-7.9(m)

Note) *: Yield is shown in terms of % by weight relative to the starting compound.
**: The number of sulfate groups in the molecule to be calculated from the elementary analysis value.
***: Mixture of compound (ℓ = 3)/compound (ℓ = 4) = 1:1

Table 4



(II)

Example No.	Compound (II)				Physical property value etc.			
	R^6 and R^7	ℓ	Number of sulfate group**	Kind of salt	Form	Yield (%)*	IR ν_{max}^{Nujol} cm^{-1}	^1H-NMR (D_2O) δ
36	R^6: $-CH_3$ R^7: $-CH_2CH_2NHCOCH_2$	1	16	K	Light brown powder	224	1640, 1550, 1240, 1040, 1000, 940, 810, 740, 620, 580	1.7-2.3(m)
37	"	3	13	"	White powder	191	1640, 1550, 1430, 1240, 1040, 1000, 940, 810, 740, 620, 580	1.99(br,s) 2.18(br,s),
38	R^6:  R^7: $-CH_2CH_2NHCO-$	1	16	"	Light brown powder	235	1640, 1550, 1240, 1040, 1000, 940, 880, 810, 740, 690, 580	7.1-8.0(m)

(to be continued)

39	"	2	15	K	White powder	194	1640, 1550, 1240, 1040, 1000, 940, 810, 740, 620, 580	6.8-8.0(br)
40	"	3	15	"	"	189	1630, 1550, 1430, 1240, 1160, 1040, 1000, 940, 810, 740, 620, 580	7.47(br,s)

Note) *: Yield is shown in terms of % by weight relative to the starting compound.
**: The number of sulfate groups in the molecule to be calculated from the elementary analysis value.

Example 41

To 0.5 g of heptakis(6-benzenesulfonylamino-6-deoxy)-β-cyclodextrin was added 30 ml of pyridine, and then 1.6 g of sulfur trioxide-pyridine complex was added thereto, followed by stirring at 70 °C for 6 hours.

After completion of the reaction, the supernatant was removed, and the residue was washed successively with methanol and ethanol to give a powder. The powder was collected by filtration and dried to obtain a brown powder. The powder was dissolved in 3 ml of water, and the pH of the solution was adjusted to 8 with a 10% aqueous sodium hydroxide, followed by purification on a crosslinked dextran gel: Sephadex G-10 column (trade name, manufactured by Pharmacia AB) to give 0.7 g of sodium salt of heptakis(6-benzenesulfonylamino-6-deoxy)-β-cyclodextrin·polysulfate as a white powder.

Yield = 140% (in terms of wt% of the desired product relative to the starting compound. The same applies also in Examples 42 to 54.)

$$\mathrm{IR}\ \nu_{max}^{Nujol}\,\mathrm{cm}^{-1}\quad :$$

1240, 1160, 1050, 830

^{1}H-NMR(D_2O)δ : 7.0-8.2(br, s)

The number of sulfate groups in the molecule to be calculated from the elementary analysis value: 11.

Example 42

In 85 ml of pyridine was dissolved 0.83 g of mono(6-benzenesulfonylamino-6-deoxy)-β-cyclodextrin with heating at 100°C, and 6.2 g of sulfur trioxide-pyridine complex was added thereto with stirring well, followed by stirring at 100°C for 6 hours. The pyridine was removed by evaporation, and the residue was dissolved in 20 ml of water and 40 ml of methanol, followed by further addition of 300 ml of methanol. The resulting mixture was allowed to stand overnight at a cool place, and the precipitates thus formed were collected by filtration, washed with methanol and dissolved in water. The resulting solution was concentrated to evaporate the methanol contained therein. Water and 50 ml of a strongly acidic ion exchange resin S-1B-(H^+) (trade name, manufactured by Mitsubishi Kasei Corporation) were added to the residue, and the resulting mixture was stirred at room temperature for 30 minutes. The resin was removed by filtration from the mixture, and after the pH of the filtrate was adjusted to 7.3 with 1.7N potassium hydroxide, the filtrate was filtered through a membrane filter, followed by freeze drying to give 2.0 g of potassium salt of mono(6-benzenesulfonylamino-6-deoxy)-β-cyclodextrin·polysulfate as a white powder.

Yield: 241%

$$\mathrm{IR}\ \nu_{max}^{KBr}\,\mathrm{cm}^{-1}\quad :$$

1640, 1240, 1160, 1000, 940, 810

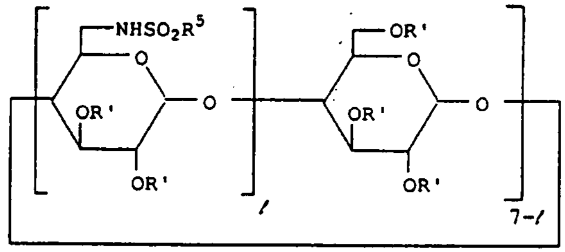
^{1}H-NMR(D_2O)δ : 7.6-8.1(m)

The number of sulfate groups in the molecule to be calculated from the elementary analysis value : 19

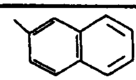
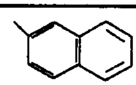
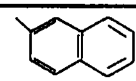
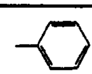
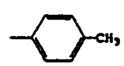
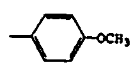
Examples 43 to 54

The corresponding starting compounds were treated in the same manner as in Example 41 or 42 to obtain the compounds as listed in the following Table 5.

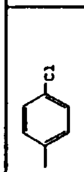
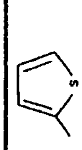
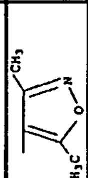
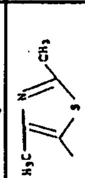
Table 5



(II)

Example No.	Compound (II)				Physical property value etc.			
	R^5	ℓ	Number of sulfate group*	Kind of salt	Form	Yield (%)	IR ν_{max}^{Nujol} cm^{-1}	^{1}H-NMR (D_2O) δ
43		2	15	K	Colorless powder	180	1640, 1240, 1160, 1000, 940, 810	7.1-8.7(br,m)
44		1	"	"	"	233	1640, 1240, 1060, 1040, 1000, 940, 810	7.4-8.7(br,m)
45		** 3.5	"	"	"	167	1640, 1240, 1160, 1040, 1000, 820	6.5-8.7(br,m)
46		"	14	"	"	186	1640, 1240, 1000, 810	7.3-8.0(br,m)
47		7	11	Na	Light brown powder	113	1240, 1160, 1040, 820	2.25(br,s), 6.8-8.0(br)
48		"	8	"	Grayish powder	80	1600, 1240, 1160, 1040, 830	6.7-7.3(br,m), 7.4-8.0(br,m)

(to be continued)

49		7	9	Na	Light brown powder	96	1240, 1160, 1040, 830	7.0-7.9(br)
50		"	10	"	"	133	1400, 1240, 1160, 1040, 830	7.1(br), 7.6(br,s), 7.8(br)
51		"	10	"	"	145	1590, 1260, 1120, 830	2.3(br,s), 2.6(br,s)
52		"	8	"	"	80	1520, 1240, 1050, 830	2.45(s), 2.6(br,s)
53	$-(CH_2)_7CH_3$	"	12	"	"	90	1240, 1150, 1040, 830	0.91(brs), 1.38(brs), 1.85(br)
54	$-(CH_2)_7CH_3$	1	15	K	Colorless powder	236	1240, 1000, 940, 810	0.7-1.1(br,m), 1.3(br,s)

Note) *: The number of sulfate groups in the molecule to be calculated from the elementary analysis value.

**: Mixture of compound (ℓ = 3)/compound (ℓ = 4) = 1:1

Example 55

To 0.9 g of heptakis(6-benzylamino-6-deoxy)-β-cyclodestrin was added 60 ml of pyridine, and then 5.13 g of sulfur trioxide-pyridine complex was added thereto, followed by reaction at 70°C for 6 hours. The

supernatant was removed from the reaction mixture, and the residue was treated with methanol to give a powder. The powder was collected by filtration, dried and then dissolved in 10 ml of water. After the pH of the resulting solution was adjusted to 8 with a 10% aqueous sodium hydroxide, the solution was purified on a column packed with Sephadex G-10 (trade name, manufactured by Pharmacia AB) to give 1.17 g of sodium salt of heptakis(6-benzylamino-6-deoxy)-β-cyclodextrin polysulfate as a light brown powder.

$$IR\ \nu_{max}^{Nujol}\ cm^{-1} \quad :$$

1240, 1040, 830

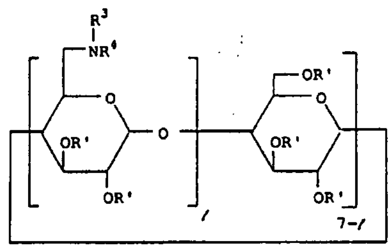
^{1}H-NMR(D_2O)δ : 7.35(br, s)

The number of sulfate groups in the molecule to be calculated from the elementary analysis valve: 14

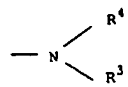
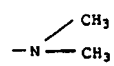
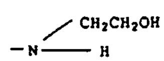
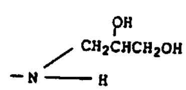
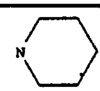
Examples 56 to 66

The corresponding starting compounds were treated in the same manner as in Example 55 to obtain the compounds as listed in the following Table 6.

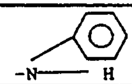
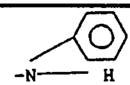
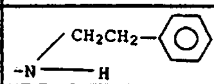
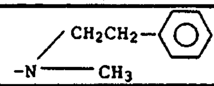
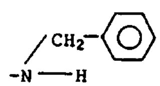
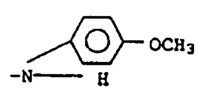
Table 6



(II)

Example No.	Compound (II)				Physical properties etc.			
		l	Number of sulfate group**	Kind of salt	Form	Yield (%) *	IR V_{max}^{Nujol} cm^{-1}	^{1}H-NMR(D_2O) δ
56		7	12	Na	Light brown powder	120	1240, 1040, 820	3.0(br,s)
57		"	20	"	Light yellow powder	140	1240, 1000, 830	3.0-3.4(br) 4.0-5.6(br,m)
58		"	18	"	Brown powder	150	1250, 1040, 820	2.8-5.6(br)
59		"	12	--	Light brown powder	83	1240, 1040, 820	1.4-2.1(br,s), 2.1-2.6(br,m)

(to be continued)

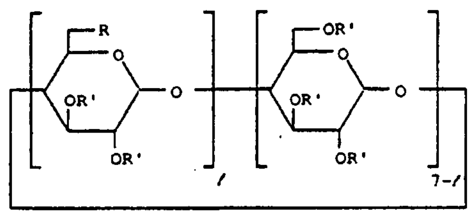
60		7	14	Na	Light brown powder	100	1240, 1040, 820	1.0-2.5(br,m)
61		"	14	"	Brown powder	100	1240, 1040, 830	6.2-7.4(br,m)
62		"	14	"	Grayish powder	90	1240, 1040, 830	7.2(br,s)
63		"	14	"	Light yellow powder	114	1240, 1040, 820	2.1(br,s), 7.2(br,s)
64		1	13	K	Colorless powder	144	1240, 1040, 820	7.5(br,s)
65	"	2	17	"	"	226	1240, 1040, 1000, 810	7.5(br,s)
66		7	13	Na	Light brown powder	66.7	1240, 1040, 830	3.0-5.5(br,m), 3.6(s), 6.2-7.8(m)

Note) *: Yield is shown in terms of % by weight relative to the starting compound.
**: The number of sulfate groups in the molecule to be calculated from the elementary analysis value.

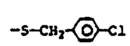
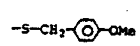
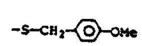
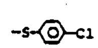
Examples 67 to 84

The corresponding starting compounds were treated in the same manner as in Example 1 or Example 42 to give the compounds as listed in the following Table 7.

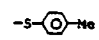
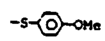
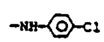
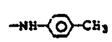
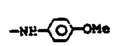
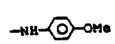
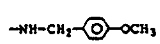
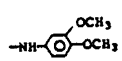
Table 7



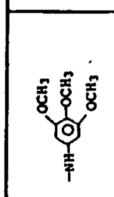
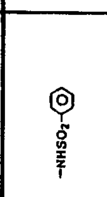
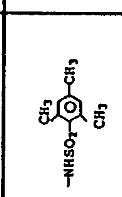
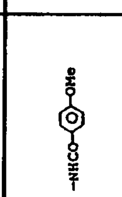
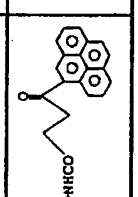
(II)

Example No.	Compound (II)				Physical properties etc.			
	R	ℓ	Number of sulfate group**	Kind of Salt	Form	Yield (%)*	IR ν_{max}^{Nujol} cm^{-1}	^1H-NMR(D_2O) δ
67		3	18	K	Colorless powder	160	1640, 1493, 1250, 1145, 1041, 950, 826	6.5-7.5(m)
68		3	18	K	"	212	1640, 1510, 1240,1160, 1030, 945, 822	3.74(s), 6.5-7.1(m), 7.1-7.5(m)
69		7	9	Na	Faintly yellow powder	80	1620, 1510, 1250, 1150 1040, 830	3.7(br), 6.6-7.5(br)
70		7	11	Na	Faintly brown powder	93	1640, 1240, 1040, 820	7.0(br,s)

(to be continued)

71		7	14	Na	Faintly brown powder	116	1640, 1500, 1240, 1040, 840	2.1(br,s), 6.95(br,s)
72		7	12	Na	"	67	1650, 1600, 1500, 1240, 1040, 830	3.6(br,s), 6.2-7.6(br,s)
73	$-NHCH_2CH_2NH_2$	1	15	Na	Colorless powder	186	1240, 1050, 820	3.1-5.6(m)
74		7	11	Na	Brown powder	36.4	1630, 1600, 1500, 1240, 1040, 820	6.0-7.0(br,m)
75		7	12	Na	Faintly brown powder	43	1630, 1510, 1240, 1040, 820	2.0-2.6(br,s), 6.6-7.8(br)
76		1	16	Na	"	167	1640, 1515, 1240, 1160, 1040, 1000, 940, 880, 820	3.85(br,s), 6.7-7.3(m)
77		3	14	K	"	138	1640, 1515, 1240, 1140, 1020, 940, 820	3.78(br,s), 6.2-7.1(m)
78		7	16	Na	"	150	1640, 1610, 1510, 1240, 1000, 820	2.5(br), 6.5-7.7(br)
79		7	14	Na	Brown powder	60	1620, 1520 1230, 1040, 820	3.7(br) 6.0-7.2(m)

(to be continued)

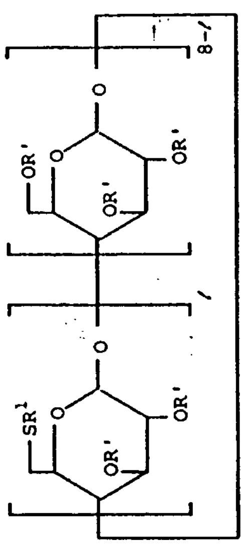
80		7	13	Na	Faintly blackish brown powder	70	1610, 1510, 1240, 1040, 820	3.45(br) 5.9(br)
81		7	12	Na	Brown powder	103	1640, 1240, 1050, 830	7.6(br,s)
82		7	11	Na	Faintly brown powder	96.7	1650, 1600, 1240, 1040, 830	2.0-2.7(br,s), 6.6-7.1(br,s)
83		7	12	Na	"	133	1650, 1610, 1500, 1260, 1040, 840	3.5(s), 6.5(br,s), 7.4(br,s)
84		2	16	K	Faintly yellow powder	192	1650, 1550, 1240, 1040, 940, 820	2.5-3.0(m), 7.0-8.5(m)

Examples 85 to 88

Each of tris(6-benzylthio-6-deoxy)-γ-cyclodextrin and octakis(6-benzylthio-6-deoxy)-γ-cyclodextrin which were obtained in Referential Example 80 was treated in the same manner as in Example 5 to obtain the

compounds as listed in the following Table 8.

Table 8



(I)

Example No.	Compound (I)				Physical properties etc.			
	R^1	l	Number of sulfate group	Kind of Salt	Form	Yield (%)	IR ν_{max}^{Nujol} cm^{-1}	^1H-NMR (D_2O) δ
85*	$-CH_2-C_6H_5$	3	19	K	Colorless powder	225	1240, 1040, 1000, 940, 810	7.39 (br, s)
86*	$-CH_2-C_6H_5$	3	19	K	"	230	1240, 1040, 1000, 940, 810	7.37 (br, s)
87*	$-CH_2-C_6H_5$	3	19	K	"	225	1240, 1040, 1000, 940, 815	7.38 (br, s)
88	$-CH_2-C_6H_5$	8	14	K	"	79	1240, 1035, 980, 825	6.0-7.2 (m)

Note) *: regio isomers

Example 89

Hexakis(6-p-tolylthio-6-deoxy)-α-cyclodextrin was treated in the same manner as in Example 5 to give sodium salt of hexakis(6-p-tolylthio-6-deoxy)-α-cyclodextrin polysulfate as a white powder.

Yield = 126 %

$$IR\nu^{Nujol}_{max}\ cm^{-1}:$$

1240, 1040, 830

^{1}H-NMR (D_2O)δ: 2.0 (br.s), 6.5 - 7.2 (br)

The number of sulfate groups in the molecule to be calculated from the elementary analysis values; 10

Example 90

Hexakis[6-(2-thenoylamino)-6-deoxy]-α-cyclodextrin was treated in the same manner as in Example 18 to give sodium salt of hexakis[6-(2-thenoylamino)-6-deoxyl-α-cyclodextrin polysulfate as a white powder.

Yield = 77.5 %

$$IR\nu^{Nujol}_{max}\ cm^{-1}:$$

1630, 1550, 1240, 1040, 1000, 830

^{1}H-NMR (D_2O)δ: 6.7(br), 7.4(br)

The number of sulfate groups in the molecule to be calculated from the elementary analysis values; 10

Referential Example 1

(1) In 2.5 ℓ of pyridine was dissolved 126 g of β-cyclodextrin, and 30 g of mesitylenesulfonyl chloride was added thereto portionwise at 25°C, followed by stirring for 2 hours. Further, 6 g of mesitylenesulfonyl chloride was added threrto and the resulting mixture was stirred for 1 hour. After water was added to the resulting mixture and the mixture was allowed to stand overenight, the solvent was removed by evaporation and the residue was dissolved in 1 ℓ of water. The resulting solution was applied onto a column packed with CHP-20 RESIN (trade name, manufactured by Mitsubishi Kasei Corporation), and the column was washed successively with 10 ℓ of water, 3 ℓ of a 10% aqueous methanol and 3 ℓ of a 20% aqueous methanol, and then 3 ℓ of a 50% aqueous methanol was passed through the column to collect an eluate. Then, in a similar manner, 3 ℓ of a 80% aqueous methnol and 3 ℓ of methanol were successively passed through the column to collect respective eluates, from which the solvents were removed by evaporation and further evaporated to dryness under reduced pressure to give the following compounds i) to iii).

i) mono(6-0-mesitylenesulfonyl)-β-cyclodextrin

Yield = 52.6g (40%)

White powder

$$IR\ \nu^{Nujol}_{max}\ cm^{-1}\quad :$$

1160,1080,1030

^{1}H-NMR(DMSO-d_6)δ : 2.29(s, 3H), 2.54(s, 6H), 2.7-4.6(m, 48H), 4.6-4.9(m, 7H), 5.70(brs, 14H), 7.10(s, 2H)

ii) bis(6-0-mesitylenesulfonyl)-β-cyclodextrin

Yield = 13.0g (8.7%)

White powder

$$IR\ \nu_{max}^{KBr} cm^{-1} \qquad :$$

1610, 1355, 1160, 1030

^{1}H-NMR(DMSO-d_6)δ : 2.29(s, 6H), 2.52(s, 12H), 3.1-4.6(m, 47H), 4.74 (brs, 4H), 4.84(brs, 3H), 5.6-5.9-(m, 14H), 7.07(s, 2H), 7.10(s, 2H)

iii) tris(6-O-mesitylenesulfonyl)-β-cyclodextrin

Yield = 1.0g

White powder

$$IR\ \nu_{max}^{KBr} cm^{-1} \qquad :$$

1610, 1355, 1190, 1175, 1150, 1030

^{1}H-NMR(DMSO-d_6)δ : 2.2-2.4(m, 9H), 2.4-2.7(m, 18H), 3.0-5.0(m, 53H), 5.6-6.0(m, 14H), 7.0-7.3(m, 6H)

Referential Example 2

(1)-a In a sealed tube were stirred 26.4 g of mono(6-O-mesitylenesulfonyl)-β-cyclodextrin and 350 ml of a 10% ammonia in methanol at 70°C for 3 days. After cooling of the mixture, the crystals formed were collected by filtration and dried to give 18.1 g of mono(6-amino-6-deoxy)-β-cyclodextrin as a white powder.

Yield = 79.8%

m.p. 262°C (dec.)

$$IR\ \nu_{max}^{KBr} cm^{-1} \qquad :$$

3300, 1638, 1158, 1080, 1030

(1)-b Bis-(6-O-mesitylenesulfonyl)-β-cyclodextrin was treated in the same manner as in (1)-a to give bis-(6-amino-6-deoxy)-β-cyclodextrin.

Yield = 71%

m.p. 245°C (dec.)

$$IR\ \nu_{max}^{KBr} cm^{-1} \qquad :$$

3300, 1630, 1158, 1080, 1030

(2)-a In 10 ml of water and 10 ml of tetrahydrofuran was suspended 1.13 g of the product obtained in (1)-a, and then 0.1 g of sodium hydrogencarbonate and 0.21 g of benzenesulfonyl chloride were added thereto, followed by stirring overnight at room temperature. After concentration, the reaction mixture was cooled with ice water to effect precipitation. The crystals precipitated were collected by filtration and washed successively with water and acetone, followed by drying to give 1.0 g of mono(6-benzenesulfonylamino-6-deoxy)-β-cyclodextrin as a white powder.

Yield: 78.5%

m.p. 233 - 236°C (dec.)

^{1}H-NMR(DMSO-d_6)δ : 4.3-4.6(m, 6H), 4.7-5.0(m, 7H), 5.6-5.9(m, 14H), 7.4-7.7(m, 3H), 7.7-7.9(m, 2H)

(2)-b The product obtained in (1)-b and naphthalenesulfonyl chloride were treated in the same manner as in (2)-a to give bis(6-naphthalenesulfonylamino-6-deoxy)-β-cyelodextrin as a white powder.

Yield: 70%

^{1}H-NMR(DMSO-d_6)δ : 4.4-5.0(m), 5.0-6.2(m), 7.5-8.6(m)

Referential Example 3

To a solution of 56.8 g of β-cyclodextrin in 600 ml of pyridine stirred on a 60°C hot water bath was added dropwise a solution of 43.7 g of mesitylenesulfonyl chloride in 100 ml of pyridine over 3 hours, and the resulting mixture was further stirred for 2 hours. After the solvent was evaporated from the reaction

mixture, the residue was dissolved in 200 ml of methanol, and 300 ml of water was added thereto. Then, the resulting solution was cooled with ice water, and after the supernatant was removed, the residue was treated with acetone for pulverization. After the resulting powder was collected by filtration and dried, separation and purification were carried out by silica gel column chromatography to give the following compounds i), ii) and iii).

i) tris(6-0-mesitylenesulfonyl)-β-cyclodextrin
Yield = 7.0 g
White powder

$$\mathrm{IR}\ \nu_{max}^{KBr}\mathrm{cm}^{-1}\quad :$$

3400, 2850, 1610, 1350, 1190, 1175, 1155, 1080, 1030
^{1}H-NMR(DMSO-d_6)δ : 2.2-2.4(m, 9H), 2.4-2.7(m, 18H), 3.0-5.0(br, 53H), 5.6-6.0(m, 14H), 7.0-7.3(m, 6H)

ii) tetrakis(6-0-mesitylenesulfonyl)-β-cyclodextrin
Yield = 3.0 g
White powder

$$\mathrm{IR}\ \nu_{max}^{KBr}\mathrm{cm}^{-1}\quad :$$

3400, 2850, 1610, 1355, 1190, 1170, 1080, 1055
^{1}H-NMR(DMSO-d_6)δ : 2.27(br, s, 12H), 2.4-2.7(m, 24H), 3.0-5.0(m, 52H), 5.6-6.1(m, 14H), 6.9-7.2(m, 8H)

iii) pentakis(6-0-mesitylenesulfonyl)-β-cyclodextrin
Yield = 1.30 g
White powder

$$\mathrm{IR}\ \nu_{max}^{KBr}\mathrm{cm}^{-1}\quad :$$

3400, 2850, 1610, 1355, 1190, 1175, 1080, 1055
^{1}H-NMR(DMSO-d_6)δ : 2.26(br, s, 15H), 2.3-2.7(m, 30H), 3.0-5.0(m, 51H), 5.6-6.1(m, 14H), 6.8-7.2(m, 10H)

Referential Example 4

To a solution of 0.69 g of benzylmercaptan in 20 ml of dimethylformamide was added 0.22 g of sodium hydride (content 62%) with stirring and ice-cooling, and 1 g of heptakis(6-iodo-6-deoxy)-β-cyclodextrin was added thereto. To effect reaction the mixture was stirred overnight in an argon gas stream at room temperature. The reaction mixture was poured into 200 ml of water, and the precipitate thus formed was collected by filtration, washed and then dried to give 0.95 g of heptakis(6-benzylthio-6-deoxy)-β-cyclodextrin as a yellow powder.

^{1}H-NMR(DMSO-d_6)δ : 4.9(br,s), 5.82(br,s), 7.17(br,s)

Referential Example 5

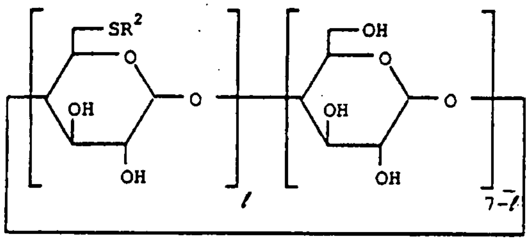
To a suspension of 1.2 g of sodium hydride (content 62%) in 130 ml of dimethylformamide was added dropwise 3.5 ml of benzylmercaptan, and after 30 minutes 13.2 g of mono(6-O-mesitylenesulfonyl)-β-cyclodextrin was added thereto, followed by stirring at 80 °C for 8 hours. After cooling, the reaction mixture was poured into 600 ml of acetone, and the precipitate thus formed was collected by filtration and then dried to give 9.84 g of mono(6-benzylthio-6-deoxy)-β-cyclodextrin as a colorless powder.

^{1}H-NMR(DMSO-d_6)δ : 4.83(br,s), 5.73(br,s), 7.2-7.4(m)

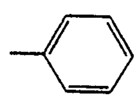
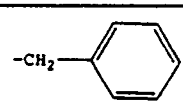
Referential Examples 6 to 16

The corresponding starting compounds were treated in the same manner as in Referential Example 5 to obtain the compounds as listed in the following Table 9.

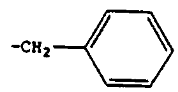
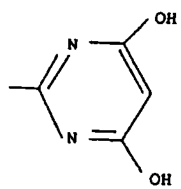
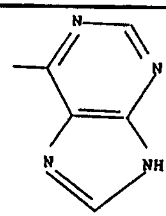
Table 9



(III)

Referential Example No.	Compound (III)		Physical properties etc.		
	R^2	l	Form	Yield (%)*	^{1}H-NMR (DMSO-d_6)
6		7	Yellow powder	95.5	4.95(br,s), 5.92(br,s) 7.0-7.3(br,s)
7	$-(CH_2)_4CH_3$	7	Light brown powder	76	0.86(br,s), 1.35(br,s) 2.54(br,s), 4.9(br,s) 5.82(br,s)
8		2	Colorless powder	82	4.85(br,s), 5.6-6.0(m) 7.1-7.4(m)
9	"	3	"	72	3.0-4.0(m), 4.4-4.7(m), 4.8-5.0(m), 5.6-6.0(m) 7.1-7.3(m)

(to be continued)

10		4	Colorless powder	51	2.5-4.0(m), 4.4-4.7(m) 4.87(br,s), 5.5-6.0(m) 7.0-7.4(m)
11	"	5	"	50	2.5-4.0(m), 4.5-4.8(m) 4.89(br,s), 5.6-6.0(m) 7.1-7.4(m)
12	$-(CH_2)_{17}CH_3$	1	"	70	0.86(t), 1.24(S), 1.4-1.6(m), 4.7-4.9(m), 5.6-5.9(m)
13	-C(ph)3	"	Light reddish brown powder	40	4.6-4.9(m), 5.2-6.0(m), 7.27(S)
14		"	Colorless powder	41	3.2-4.0(m), 4.4-4.7(m), 4.8-5.2(m), 5.6-6.0(m)
15		"	"	78	3.1-4.0(m), 4.3-4.6(m), 4.7-4.9(m), 4.96(d), 5.6-5.9(d), 5.95(d)
16	"	2	Colorless powder *	48	3.0-4.6(m), 4.6-5.2(m) 5.3-6.5(m), 8.3-8.9(m)

Note) *: Yield is shown in terms of % by weight relative to the starting compound.

Referential Example 17

To 1 g of heptakis(6-amino-6-deoxy)-β-cyclodextrin were added 30 ml of methanol and 1.7 g of benzoic anhydride, and the mixture was refluxed by heating for 18 hours. The reaction mixture was evaporated to dryness under reduced pressure, and ethyl ether was added to the residue. The insolubles were collected

by filtration and dried, followed by separation and purification by silica gel column chromatography to give 1 g of heptakis(6-benzoylamino-6-deoxy)-β-cyclodextrin as a white powder.

Yield = 61%

^{1}H-NMR(DMSO-d_6)δ : 4.96(d), 7.0-7.8(m), 7.9-8.2(br,m)

Referential Example 18

To 1 g of heptakis(6-amino-6-deoxy)-β-cyclodextrin was added 60 ml of a 10% aqueous sodium hydrogencarbonate solution, and 1.4 g of 2-thenoyl chloride was further added dropwise thereto. After the mixture was vigorously stirred at room temperature for 3 days, the precipitate thus formed was collected by filtration, washed and dried, followed by separation and purification by silica gel column chromatography to give 0.6 g of heptakis[6-(2-thenoylamino)-6-deoxy]-β-cyclodextrin as a white powder.

Yield = 59%

^{1}H-NMR(DMSO-d_6)δ : 3.1-4.0(br,m), 5.0(br,s), 5.9(br,s), 5.95(br,s), 6.86(dd), 7.55(d), 7.70(d), 8.10(br,s)

Referential Example 19

In 20 ml of methanol was suspended 2.27 g of mono(6-amino-6-deoxy)-β-cyclodextrin, and then 1.38 g of 3,5-diacetoxybenzoic anhydride was added thereto, followed by refluxing with heating for 8 hours. After the mixture was cooled, 20 ml of conc. ammonia water was added thereto, and the mixture was stirred at room temperature overnight. The solvent was removed by evaporation, and after the residue was washed, the crude product was collected by filtration and dissolved in water. The resulting solution was passed through a column packed with a CHP-20 RESIN (trade name; manufactured by Mitsubishi Kasei Corporation). The column was washed successively with 500 ml of water and 500 ml of a 10% aqueous methanol, and then a 50% aqueous methanol was passed through the column to collect the eluate. The solvent was evaporated off, and the residue was washed and then dried to give 2.22 g of mono[6-deoxy-6-(3,5-dihydroxybenzoylamino)]-β-cyclodextrin as a white powder.

Yield = 87%

^{1}H-NMR(DMSO-d_6)δ : 4.3-4.6(m), 4.7-5.0(m), 5.5-5.9(m), 6.34(t), 6.64(d), 7.92(t), 9.40(s)

Referential Example 20

In 10 ml of chloroform was suspended 0.46 g of anisic acid, and then 0.42 ml of triethylamine was added thereto to dissolve the solid content. To the solution was added, with stirring and ice-cooling, 0.29 ml of ethyl chlorocarbonate, and the mixture was stirred for 15 minutes to give the mixed acid anhydride. After 2.26 g of mono(6-amino-6-deoxy)-β-cyclodextrin was dissolved in 20 ml of pyridine, a chloroform solution of the above mixed acid anhydride was added thereto with ice-cooling and stirring, followed by stirring at room temperature overnight. The solvent was removed by evaporation, and after the residue was washed, the resulting powder was collected by filtration, dissolved in 50 ml of 0.2N aqueous potassium hydroxide and heated at 90°C for 30 minutes. The resulting solution was cooled and made acidic with hydrogen chloride, followed by passing through a column packed with a CHP-20-RESIN (trade name; manufactured by Mitsubishi Kasei Corporation). The column was washed successively with 500 ml of water and 1 ℓ of a 30% aqueous methanol to collect the eluate. The solvent was evaporated off, and the residue was washed and then dried to give 0.71 g of mono[6-deoxy-6-(4-methoxybenzoylamino)]-β-cyclodextrin as a white powder.

Yield = 28%

^{1}H-NMR(DMSO-d_6)δ : 3.80(s), 4.3-4.6(m), 4.7-5.0(m), 5.4-5.9(m), 6.36(d), 7.79(d), 8.0-8.2(br)

Referential Example 21

(1) In 1.2 ℓ of pyridine was dissolved 114 g of β-cyclodextrin, and then 52 g of 2-naphthylsulfonyl chloride was added thereto with stirring and ice-cooling, followed by stirring at room temperature for 24 hours. After the reaction was quenched by pouring water to the reaction mixture, the solvent was removed by evaporation and 1 ℓ of water was added to the residue, followed by heating to give a caramel-like product. The product was washed, dissolved in 1.5 ℓ of a 70% aqueous methanol with heating. After the solution was concentrated to about 1 ℓ, the precipitates thus formed were collected by filtration and dissolved in a 70% aqueous methanol with heating. After the insolubles were removed, the filtrate was left to stand, and the thus precipitated crystals were collected by filtration and dried to give 23.0 g of a mixture of tris[6-O-(2-naphthylsulfonyl)]-β-cyclodextrin/tetrakis-[6-O-(2-naphthanalenesulfonyl)-

]-β-cyclodextrin = 1:1 as a white powder.

Yield = 13%

$$\mathrm{IR}\ \nu_{max}^{Nujol}\ cm^{-1}\ :$$

1350, 1160, 1080, 1030

^{1}H-NMR(DMSO-d_6)δ : 7.5-8.5(br, m, 24H)

(2) The product obtained in (1) was treated in the same manner as in Referential Example 2-(2)-a to give a mixture of tris(6-amino-6-deoxy)-β-cyclodextrin tetrakis(6-amino-6-deoxy)-β-cyclodextrin = 1:1 as a white powder.

Yield = 68.8%

m.p. >220°C

$$\mathrm{IR}\ \nu_{max}^{KBr} cm^{-1}\ :$$

3300, 1630, 1155, 1080, 1030

(3) The product obtained in (2) was treated in the same manner as in Referential Example 17 or 18 to give a mixture of tris(6-stearoylamino-6-deoxy) cyclodextrin/tetrakis(6-stearoylamino-6-deoxy) cyclodextrin = 1:1 as a light brown powder.

Yield = 76%

^{1}H-NMR(DMSO-d_6)δ : 0.82(t), 0.9-1.7(m), 1.9-2.3(br), 4.2-4.6(br), 4.7-5.1(m), 5.5-6.1(m)

Referential Example 22

(1) 13.2 g of mono(6-O-mesitylenesulfonyl)-β-cyclodextrin and 100 ml of ethylenediamine were mixed, and the mixture was refluxed with heating for 6 hours and concentrated under reduced pressure. After addition of water and xylene to the reaction mixture, the resulting mixture was subjected three times to azeotropic distillation. The solvent was evaporated, and the residue was dissolved in 50 ml of water. The resulting solution was passed through a column packed with a strongly acidic ion exchange resin SK-1B-(H^+) (trade name, manufactured by Mitsubishi Kasei Corporation). After the column was washed with water, a 2N ammonium hydroxide solution was passed therethrough to collect an eluate. Solvent was evaporated from the elvates, and the residue was dried to give 4.6 g of mono(6-aminoethylamino-6-deoxy)-β-cyclodextrin as a white powder.

Yield = 39%

^{1}H-NMR(DMSO-d_6)δ : 2.4-2.7(m), 2.6-2.8(br), 2.7-3.0(m), 3.2-3.5(m), 3.5-3.9(m), 3.0-4.2(m), 4.2-5.5-(br), 4.82(br, s)

(2) In 30 ml of methanol was suspended 1.18 g of the product obtained in (1), and 0.41 g of acetic anhydride was added thereto, followed by refluxing with heating for 8 hours. The reaction mixture was evaporated to dryness, washed with acetone and dissolved in water, followed by treatment with activated carbon. The thus treated aqueous solution was poured into acetone to effect crystallization. The crystals thus formed were collected by filtration and dried to give 1.23 g of mono[6-deoxy-6-(N,N'-diacetyl-2-aminoethylamino)]-β-cyclodextrin as a white powder.

Yield = 97%

^{1}H-NMR(DMSO-d_6)δ : 1.77(s), 1.91(s), 2.8-4.0(m), 4.0-4.7(m), 4.84(br, s), 5.4-6.1(m), 7.7-8.1(m)

Referential Example 23

(1) Bis(6-O-mesitylenesulfonyl)-β-cyclodextrin and ethylenediamine were treated in the same manner as in Referential Example 22-(1) to give bis[6-(2-aminoethylamino)-6-deoxy]-β-cyclodertrin.

Yield = 36%

^{1}H-NMR(DMSO-d_6)δ : 2.3-3.0(m), 3.0-3.5(m), 3.5-4.0(m), 4.81(s), 5.0-6.2(br)

(2) The product obtained in (1) was treated in the same manner as in Referential Example 22-(2) to give bis(6-deoxy-6-(N,N'-dibenzoyl-2-aminoethylamino)]-β-cyclodextrin as a white powder.

Yield = 91% ^{1}H-NMR(DMSO-d_6)δ : 3.0-4.0(m), 4.2-4.7(m), 4.7-5.1(m), 5.6-6.2(m), 7.0-8.0(m), 8.3-8.7(m)

Referential Example 24

(1) Tris(6-O-mesitylenesulfonyl)-β-cyclodextrin and ethylenediamine were treated in the same manner as in Referential Example 22-(1) to give tris[6-(2-aminoethylamino)-6-deoxy]-β-cyclodextrin.

Yield = 27%

^{1}H-NMR(DMSO-d_6)δ : 2.3-2.7(m), 2.7-3.0(m), 3.0-3.5(m), 3.5-3.9(m), 3.9-5.5(br), 4.83(s)

(2) The product obtained in (1) was treated in the same manner as in Referential Example 22-(2) to give tris[6-deoxy-6-(N,N'-dibenzoyl-2-aminoethylamino)]-β-cyclodextrin as a white powder.

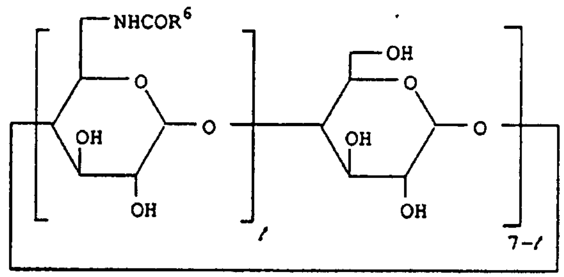
Yield = 90%

^{1}H-NMR(DMSO-d_6)δ : 2.7-4.1(m), 4.3-4.7(m), 4.7-5.2(m), 5.5-6.3(m), 6.9-7.9(m), 8.3-9.0(br)

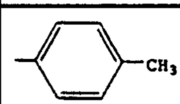
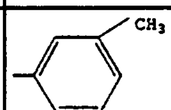
Referential Examples 25 to 36

The corresponding starting compounds were treated in the same manner as in Referential Examples 17 to 21 to obtain the compounds as listed in the following Table 10.

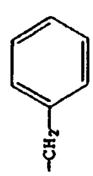
Table 10



(III)

Referential Example No.	Compound (III)		Physical properties etc.		
	R^6	ℓ	Form	Yield (%)	^{1}H-NMR(DMSO-d_6) δ
25	$-CH(CH_3)_2$	7	White powder	89	0.98(d), 4.84(d,1H), 5.5-6.3(br), 7.85(br,s)
26	$-(CH_2)_4CH_3$	"	Pale yellow powder	68	0.7-1.0(br,t), 1.0-1.7(br,m), 2.0-2.3(br,t), 4.85(br,s), 5.7-6.0(br,s), 8.0(br,s)
27	$-(CH_2)_5CH_3$	"	White powder	61	0.8-1.0(br,t), 1.1-1.7(br,m), 2.0-2.3(br,t), 4.85(br,s), 5.5-6.2(br,s), 8.0(br,s)
28		"	"	31	2.1(s), 4.95(br,s), 5.92(br,s), 6.92(d), 7.55(d), 7.98(br,s)
29		"	"	22	2.15(s), 4.95(br,s), 4.87(br,s), 7.1(br,s), 7.48(br,s), 8.05(br)

(to be continued)

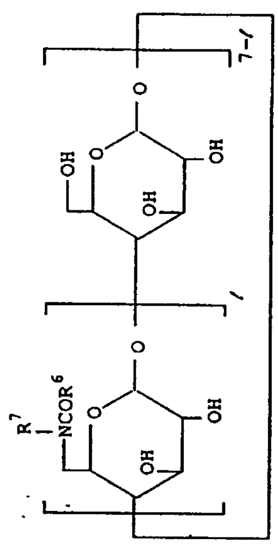
30		7	White powder	19	4.8(br,s), 5.85(br,s), 7.0(br,s), 8.25(br,s)
31	$-(CH_2)_{16}CH_3$	1	"	77	0.85(t), 1.23(s), 1.3-1.5(m), 1.9-2.3(m), 4.3-4.6(m), 4.83(br,s), 5.5-5.9(m), 7.4-7.6(br)
32	$-(CH_2)_6CH_3$	"	"	79	0.86(t), 1.23(s), 1.3-1.6(m), 2.08(t), 4.45(d), 4.85(d), 5.5-6.0(m), 7.5-7.7(m)
33	$-(CH_2)_4CH_3$	"	"	77	0.85(t), 1.1-1.6(m), 2.08(t), 4.3-4.6(m), 4.83(d), 5.5-5.9(m), 7.5-7.7(m)
34	$-(CH_2)_{16}CH_3$	2	"	76	0.85(t), 1.23(s), 1.3-1.6(m), 1.9-2.3(m), 4.3-4.6(m), 4.83(br,s), 5.6-5.9(m), 7.4-7.7(br)
35	$-(CH_2)_6CH_3$	3.5*	"	46	0.85(t), 1.22(s), 1.3-1.6(m), 1.9-2.3(m), 4.2-4.7(br), 4.7-5.0(m), 5.4-6.2(m)
36	$-(CH_2)_4CH_3$	"	"	56	0.84(br,s), 1.22(br,s), 1.3-1.7(m), 1.9-2.3(m), 4.2-4.7(m), 4.83(br,s), 5.4-6.2(m)

Note) * Mixture of compound (ℓ = 3)/compound (ℓ = 4) = 1:1

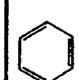
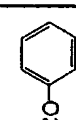
Referential Examples 37 and 38

The corresponding starting compounds were treated in the same manner as in Referential Example 22 to obtain the compounds as listed in the following Table 11.

Table 11



(III)

Referential Example No.	Compound (III): R^6 and R^7	l	Physical properties etc.: Form	Yield (%)	^1H-NMR($DMSO-d_6$) δ
37	R^6: $-CH_3$ R^7: $-CH_2CH_2NHCOCH_3$	3	White powder	90	1.7-2.1(m), 3.0-4.0(m), 4.3-4.7(m), 4.7-5.2(m), 5.6-6.2(m), 7.7-8.2(m)
38	R^6:  R^7: $-CH_2CH_2NHCO-$	1	"	82	3.0-4.1(m), 4.2-4.7(m), 4.7-5.1(m), 5.5-6.1(m), 7.2-8.0(m), 8.4-8.7(m)

Referential Example 39

To 1 g of heptakis(6-amino-6-deoxy)-β-cyclodextrin was added 40 ml of a 10% aqueous sodium hydrogen carbonate, and then 3.3 g of benzenesulfonyl chloride was added dropwise thereto, followed by

vigorous stirring at room temperature for 2 days. The precipitates thus formed were collected by filtration, washed with water and dried to give 1.3 g of heptakis(6-benzenesulfonylamino-6-deoxy)-β-cyclodextrin as a white powder.

Yield: 69%

^{1}H-NMR(DMSO-d_6)δ : 4.75(br, s), 5.7-5.9(br, s), 7.4-8.0(br, m)

Referential Example 40

(1) In 1.2 ℓ of pyridine was dissolved 114 g of β-cyclodextrin, and under stirring of the resulting solution with ice cooling, 52 g of 2-naphthalenesulfonyl chloride was added thereto. After the reaction mixture was stirred at room temperature for 24 hours, water was added thereto to quench the reaction. The solvent was removed from the reaction mixture, and 1 ℓ of water was added to the residue, followed by heating. The supernatant was decanted off, and the caramel-like substance thus obtained was washed with water and then dissolved in 1.5 ℓ of a 70% aqueous methanol with heating. The resulting solution was concentrated to about 1 ℓ, and the precipitates thus formed were collected by filtration. The precipitates were dissolved again in a 70% aqueous methanol with heating, and after the insolubles were removed by filtration, the filtrate was left to stand to allow crystallization. The crystals formed were collected by filtration and dried to give 23 g of a mixture of tris(6-O-naphthalenesulfonyl)-β-cyclodextrin/tetrakis-(6-O-cyclodestrin = 1:1 as a white powder.

Yield: 13%

$$\mathrm{IR}\ \nu_{max}^{Nujol}\,\mathrm{cm}^{-1}\quad :$$

1350, 1160, 1080, 1030

^{1}H-NMR(DMSO-d_6)δ : 7.5-8.5(br, m, 24H)

(2) The product obtained in (1) was treated in the same manner as in Referential Example 2-(2)-a to give a mixture of tris(6-amino-6-deoxy)-β-cyclodextrin/tetrakis-(6-amino-6-deoxy)-β-cyclodextrin = 1:1.

Yield: 68.8%

m.p. >220 °C

$$\mathrm{IR}\ \nu_{max}^{KBr}\,\mathrm{cm}^{-1}\quad :$$

3300, 1630, 1155, 1080, 1030

(3) The product obtained in Referential Example 21-(2) was treated in the same manner as in Referential Example 2-(3)-a to give a mixture of tris(6-benzenesulfonylamino-6-deoxy)-β-cyclodextrin/tetrakis-(6-benzenesulfonylamino-6-deoxy)-β-cyclodestrin = 1:1 as a white powder.

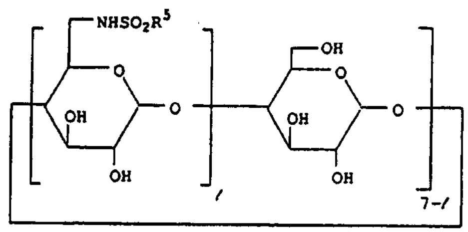
Yield: 54%

^{1}H-NMR(DMSO-d_6)δ : 4.5-5.2(m), 5.3-6.3(br), 7.4-8.1(m)

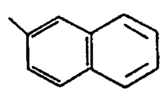
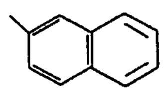
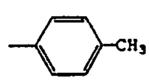
Referential Examples 41 to 50

The corresponding starting compounds were treated in the same manner as in Referential Examples 39 to 40 to obtain the compounds as listed in the following Table 12.

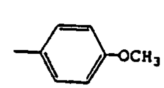
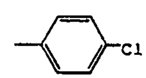
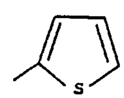
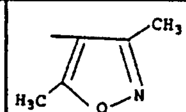
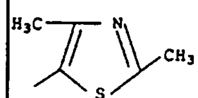
Table 12



(III)

Referential Example No.	Compound (III)		Physical properties etc.		
	R^5	ℓ	Form	Yield (%)	^{1}H-NMR(DMSO-d_6) δ
41		1	White powder	61	4.5-5.0(m), 5.0-6.5(br), 7.5-8.4(m)
42		3.5*	"	52	4.5-5.2(m), 5.4-6.2(br), 7.4-8.6(m)
43		7	"	73	2.3(s), 4.75(br,s), 5.8(br,s), 7.0(br,s), 7.2-7.8(m)

(to be continued)

44		7	Light yellow powder	43	4.75(br,s), 5.8(br,s), 6.8-7.9(br,m)
45		"	"	35	4.75(br,s),5.77(br,s), 7.2-8.0(br,m)
46		"	"	42	4.8(br,s), 5.82(br,s), 7.1(t), 7.43(br,s), 7.6(d), 7.84(d)
47		"	White powder	17	2.28(s), 2.5(s), 4.8(br,s), 5.8(br,s)
48		"	Light yellow powder	19	2.45(s), 2.60(s), 4.74(br,s), 5.8(br,s), 7.46(br,s)
49	$-(CH_2)_4CH_3$	"	White powder	12	0.85(t), 1.28(s), 1.7(br,s), 4.95(br,s), 5.8(br,s), 6.55(br,s)
50	$-(CH_2)_{16}CH_3$	1	"	39	0.88(t), 1.25(s), 1.5-1.8(m), 4.83(d), 4.94(d), 5.0-6.3(br)

Note) *: Mixture of compound (ℓ = 3)/compound (ℓ = 4) = 1:1

Referential Example 51

To 2 g of heptakis(6-O-mesitylenesulfonyl)-β-cyclodextrin was added 15 mℓ of benzylamine to effect reaction at 80 to 90°C for 3 hours. To the reaction mixture was added 150 mℓ of water, and the

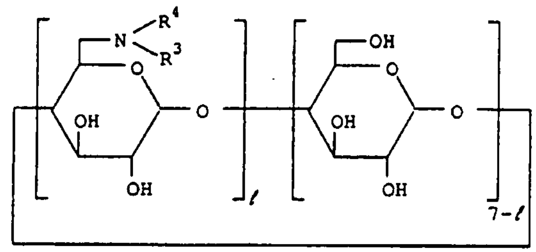
precipitates thus formed were collected by filtration, washed with water and dried to give 1.1 g of heptakis-(6-benzylamino-6-deoxy)-β-cyclodextrin as a white powder.

^{1}H-NMR(DMSO-d_6)δ : 2.83(br), 4.85(br, d), 5.8(br, s), 7.18(br, s)

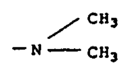
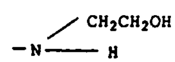
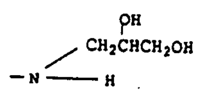
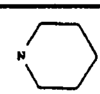
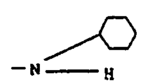
Referential Examples 52 to 62

Mono(6-O-mesitylenesulfonyl)-β-cyclodestrin, bis(6-O-mesitylenesulfonyl)-β-cyclodestrin or heptakis(6-O-mesitylenesulfonyl)-β-cyclodestrin were treated with the corresponding amine compounds in the same manner as in Referential Example 51 to give the compounds as listed in the following Table 13.

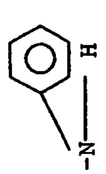
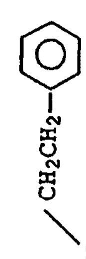
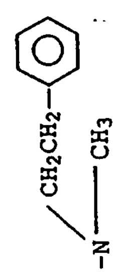
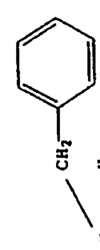
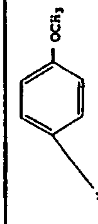
Table 13



(III)

Referential Example No.	Compound (III)		Physical properties etc.		
		ℓ	Form	Yield (%)	1H-NMR(DMSO-d6)
52		7	White powder	68	2.15(s), 4.84(br,s), 5.71(br,s)
53		"	Pale yellow powder	80	2.6(br,t), * 2.82(br,m) 4.77(d)
54		"	White powder	50	2.85(br,s), 4.86(br,s)
55		"	Yellow powder	75	1.45(br,s), 2.0-3.0(br), 4.85(br,s), 5.82(br,s)
56		"	Light brown powder	79	1.1(br,s), 1.65(br,s), 4.83(br,s), 5.67(br,s)

(to be continued)

57		7	Brown powder	53	3.0-4.1(m), 4.9(br,s), 5.2-5.8(br,s) 6.4-7.4(m)
58		"	White powder	69	2.71(br,s), 2.9(br,s), 3.31(br,s), 4.8(br,s), 5.73(br,s), 7.11(br,s)
59		"	Light brown powder	50	2.20(br,s), 2.6(br,s), 3.30(br,s), 4.8(br,s), 5.78(br,s), 7.15(br,s)
60		1	White powder	84	3.2-3.9(m), 4.3-4.6(m), 4.7-4.9(m), 5.6-5.9(m), 7.1-7.4(m)
61	"	2	"	59	3.2-3.9(m), 4.3-4.7(m), 4.7-5.0(m), 5.5-5.9(m), 7.1-7.4(m)
62		7	Brown powder	81.5	3.1-4.2(br,m), 3.52(s), 4.95(s), 6.54(s)

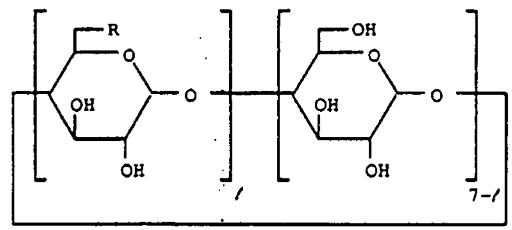
Note) *: Values are measured at ^{1}H-NMR(D_2O)δ

Referential Examples 63 to 79

The corresponding starting compounds were treated in the same manner as in Referential Example 2, Referential Example 5, Referential Example 20 or Referential Example 51 to give the compounds as listed

in the following Table 14.

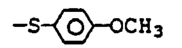
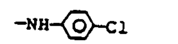
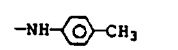
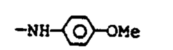
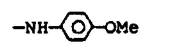
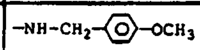
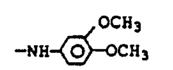
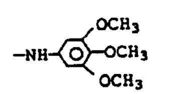
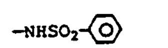
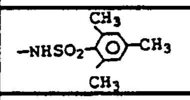
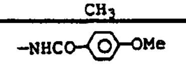
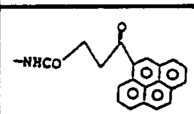
Table 14



(III)

Referential Example No.	Compound (III)		Physical properties etc.		
	R	ℓ	Form	Yield (%)*	^{1}H-NMR (DMSO-d_6)
63	$-S-CH_2-C_6H_4-Cl$	3	Colorless powder	64	2.5-4.0(m), 4.5-4.8(m), 4.8-5.1(m), 5.5-6.1(m), 7.2-7.6(m)
64	$-S-CH_2-C_6H_4-OMe$	3	"	67	2.5-4.2(m), 3.70(s), 4.4-4.8(m), 4.8-5.0(m), 5.6-6.0(m), 6.7-6.9(m), 7.0-7.3(m)
65	$-S-CH_2-C_6H_4-OCH_3$	7	White powder	84.2	3.7(s), 4.90(br.s), 6.8(br.s) 7.15(br.d)
66	$-S-C_6H_4-Cl$	7	Light yellow powder	100	4.95(br.s), 7.1(s)
67	$-S-C_6H_4-CH_3$	7	"	75.8	2.14(s), 4.95(br,s), 6.8-7.4(m)

(to be continued)

68		7	Light yellow powder	100	3.55(s), 4.9(br,s), 6.6-7.5(m)
69		7	Brown powder	42	4.85(br,s), 6.5(d), 6.9(d)
70		7	Blakish brown powder	69	2.1(s), 5.9(br,s), 6.3-6.6(d) 6.6-6.8(d)
71		1	Colorless powder	64	3.1-4.3(m), 3.62(s), 4.4-4.8(m), 4.84(br,s), 5.6-6.2(m), 6.59(d), 6.69(d)
72		3	Light brown powder	42	3.0-4.0(m), 4.7-5.0(m), 5.5-6.1(m), 6.4-6.8(m)
73		7	"	51.0	2.75(br,s), 4.82(br,s), 6.6-7.2(m)
74		7	Blakish brown powder	40	3.43(s), 3.50(s), 4.90(br,s) 5.75(br,s), 6.2-6.9(m)
75		7	"	45	3.47(s), 4.90(br,s), 5.90(d)
76		7	White powder	69	4.75(br,s), 7.4-8.0(br,m)
77		7	"	52.8	2.20(s), 2.40(s), 4.5(br,s), 6.7(br,s), 6.9(s)
78		7	"	44	3.3(s), 4.9(br,s), 6.5(d), 7.6(d)
79		2	Light yellow powder	97	2.5-2.9(m), 3.1-4.0(m), 4.4-5.1(m), 5.6-6.0(m), 7.7-7.9(br), 8.0-8.7(m)

Referential Example 80

(1) In 600 ml of pyridine was suspended 39.1 g of a dried γ-cyclodextrin, and 26 g of mesitylenesulfonyl chloride was added thereto under stirring at room temperature, followed by stirring at room temperature

overnight. Water was added to the reaction mixture and the mixture was evaporated to remove solvent. The residue was washed with water and then with ethanol. The resultant powder was collected by filtration, and dissolved in methanol. The solution was applied onto a column packed with CHP-20 RESIN (trade name, manufactured by MITSUBISHI KASEI Corporation), and the column was washed with 50 % methanol and then with 65 % methanol. Then, 80 % methanol was passed through the column to elute tris(6-O-mesitylenesulfonyl)-γ-cyclodextrin, and then methanol was passed through the column to elute tetrakis(6-O-mesitylenesulfonyl)-γ-cyclodextrin.

(2) The 80 % methanol eluate was evaporated to dryness, and the residue was dissolved in methanol. The solution was applied onto a column packed with CHP-20 RESIN (trade name, manufactured by MITSUBISHI KASEI Corporation), and the column was washed with 70 % methanol. Then 80 % methanol was passed through the column to collect three fractions (fraction A, B and C).

The retention time of each fraction was examined by high performance liquid chromatography. The results are as follows.

Fraction A; (retention time) 7.4, 9.0, 9.5, 11.5 (min)
Fraction B; (retention time) 11.6 (min)
Fraction C; (retention time) 7.4 (min)

Each of fractions was evaporated to dryness, whereby the following products (i.e., regio isomers of tris (6-O-mesitylenesulfonyl)-γ-cyclodextrin.) were obtained as colorless powder.

(a) Tris (6-O-mesitylenesulfonyl)-γ-cyclodextrin prepared from fraction A
Yield 5.0 g
m.p. 188 °C (decomposed)

(b) Tris(6-O-mesitylenesulfonyl)-γ-cyclodextrin prepared from fraction B
Yield 1.12g
m.p. 192 °C (decomposed)

(c) Tris(6-O-mesitylenesulfonyl)-γ-cyclodextrin prepared from fraction C
Yield 1.20g
m.p. 190 °C (decomposed)

On the other hand, the methanol eluate obtained in paragraph (1) was evaporated to dryness. The residue (i.e., crude tetrakis(6-O-mesitylenesulfonyl)-γ-cyclodextrin were dissolved in 100 ml of pyridine and 7.2 g of mesitylenesulfonyl chloride were added thereto. The mixture was stirred at room temperature for 2 days. Then, the reaction mixture was evaporated to dryness, and the residue was purified by silica gel column chromatography to give 0.93 g of octakis(6-O-mesitylenesulfonyl)-γ-cyclodextrin as colorless powder.

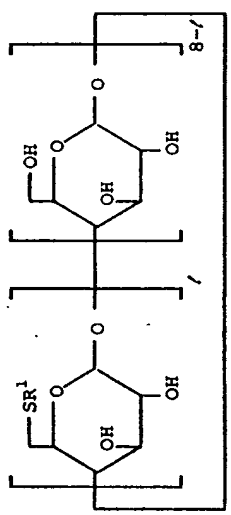
m.p. 230 °C (decomposed)

(3) To a mixture of 0.49 g of benzylmercaptane, 10 ml of N,N-dimethylformamide and 0.17 g of 60% sodium hydride was added 1.0 g of tris(6-O-mesitylenesulfonyl)-γ-cyclodextrin (obtained from fraction A). The mixture was stirred at 80 °C for 2 hours. After cooling, water was added to the mixture, and the precipitates were collected by filtration and dissolved in methanol. The methanol solution was treated with activated charcoal and then condensed. Acetone was added to the residue, and the precipitates were collected by filtration. The crude product (0.51 g) thus obtained was dissolved in N,N-dimethylformamide, and the solution was applied on a column packed with Sephadex G-25 (trade name, manufactured by Pharmacia AB). The eluate with N,N-dimethylformamide was evaporated to dryness, and the residue was washed with acetone and then dried. 0.28 g of tris(6-benzylthio-6-deoxy)-γ-cyclodextrin was obtained as coloreless powder.

m.p. 233 °C (decomposed)

Each of tris(6-O-mesitylenesulfonyl)-γ-cyclodextrin (obtained from fraction B and C) was treated in the same manner as above to obtain the compounds as listed in the following Table 15.

Table 15



(II)

Referential Example No.	Compound (II) R^1	Compound (II) l	Physical properties etc. Form	Yield (%)	^1H-NMR (DMSO-d_6) δ
80* (3)	$-CH_2-C_6H_5$	3	Colorless powder	30	2.5-3.1(m), 3.3-4.0(m), 4.4-4.3(m), 4.91(br,s), 5.5-6.1(m), 7.23(br,s)
80* (3)	$-CH_2-C_6H_5$	3	"	27	2.5-3.1(m), 3.2-4.0(m), 4.4-4.3(m), 4.91(br,s), 5.6-6.1(m), 7.1-7.4(m)
80 (3)	$-CH_2-C_6H_5$	8	"	44	2.6-3.9(m), 4.94(s), 5.7-6.1(m), 7.15(br,s)

* Regio isomers of the compound prepared from fraction A. (obtained in Referential Example 80(3))

Referential Example 81

To a mixture of 0.83 g of p-toluenethiol, 30 ml of N,N-dimethylformamide and 0.25 g of 62.7 % sodium hydride was added 1 g of hexakis (6-bromo-6-deoxy)-α-cyclodextrin, and the mixture was stirred in argon

gas stream at room temperature for 20 hours. The reaction mixture was poured into 200 ml of water, and the precipitates were collected by filtration, washed and then dried to give 1.0 g of hexakis(6-p-tolylthio-6-deoxy)-α-cyclodextrin as a white powder.

m.p. 232-235 °C (decomposed)

Referential Example 82

To 0.6 g of hexakis (6-amino-6-deoxy)-α-cyclodextrin hydrochloride was added 60 ml of an aqueous 10 % sodium bicarbonate solution, and 0.6 g of 2-thenoyl chloride was added thereto. The mixture was stirred at room temperature for 3 days, the precipitates was collected by filtration, washed and dried to give 0.54 g of hexakis [6-(2-thenoylamino)-6-deoxy]-α-cyclodextrin as white powder.

m.p. 258-260 °C (decomposed)

Test Example

HIV proliferation inhibitory action

(Principle)

It is known that when MT-4 cells, which are sustaining infectious cell line of human T-cell Leukemia virus I type [HTLV-I], are infected with HIV, HIV proliferates rapidly and the MT-4 cells are killed in 5 to 6 days due to the cellular damage. Therefore, HIV proliferation inhibitory action can be evaluated by examining the number of vial cells of the MT-4 cells infected with HIV.

(Procedure)

MT-4 cells were infected with HIV (a culture supernatant of TALL-1/LAV-1) at 37 °C for one hour so that $TCID_{50}$ (median tissue culture infectious dose)/cell might be 0.001, followed by washing with the medium. The infected MT-4 cells were then suspended at a concentration of 1×10^5 cells/ml in RPMI-1640 culture media [containing 10% of FCS (fetal calf serum)] containing samples of various concentrations respectively. Each of the thus obtained cell suspension was introduced in a flat-bottom culture plate and was incubated at 37 °C in the presence of 5% carbon dioxide for 5 days. After incubation, the number of viable cells in the cell suspension was counted by the Tripan-Blue Staining Method. The HIV proliferation inhibitory action of the sample was evaluated in terms of the concentration of the sample which suppresses by 100% (completely) the infectiousness and the cell modification action of HIV.

(Results)

The results are shown in the follwing Table 16

Table 16

Test compound	HIV proliferation inhibitory action, 100% inhibition concentration (μg/ml)
Polysulfate compound prepared in Example 2 (Potassium salt)	1.9
Polysulfate compound prepared in Example 8 (Potassium salt)	3.9
Polysulfate compound prepared in Example 9 (Potassium salt)	1.95
Polysulfate compound prepared in Example 10 (Potassium salt)	0.98
Polysulfate compound prepared in Example 11 (Potassium salt)	2.98
Polysulfate compound prepared in Example 12 (Potassium salt)	3.9
Polysulfate compound prepared in Example 13 (Potassium salt)	3.9
Polysulfate compound prepared in Example 17 (Potassium salt)	1.95
Polysulfate compound prepared in Example 18 (Sodium salt)	3.9
Polysulfate compound prepared in Example 20 (Sodium salt)	3.9
Polysulfate compound prepared in Example 22 (Sodium salt)	3.9
Polysulfate compound prepared in Example 25 (Sodium salt)	3.9
Polysulfate compound prepared in Example 27 (Potassium salt)	1.95
Polysulfate compound prepared in Example 28 (Potassium salt)	1.95
Polysulfate compound prepared in Example 29 (Potassium salt)	3.9
Polysulfate compound prepared in Example 30 (Potassium salt)	3.9

(to be continued)

Test compound	HIV proliferation inhibitory action, 100% inhibition concentration (μg/ml)
Polysulfate compound prepared in Example 32 (Potassium salt)	1.95
Polysulfate compound prepared in Example 33 (Potassium salt)	1.95
Polysulfate compound prepared in Example 34 (Potassium salt)	3.9
Polysulfate compound prepared in Example 35 (Potassium salt)	3.9
Polysulfate compound prepared in Example 36 (Potassium salt)	3.9
Polysulfate compound prepared in Example 37 (Potassium salt)	3.9
Polysulfate compound prepared in Example 38 (Potassium salt)	1.95
Polysulfate compound prepared in Example 41 (Sodium salt)	3.9
Polysulfate compound prepared in Example 42 (Potassium salt)	3.9
Polysulfate compound prepared in Example 43 (Potassium salt)	1.95
Polysulfate compound prepared in Example 44 (Potassium salt)	1.95
Polysulfate compound prepared in Example 45 (Potassium salt)	1.95
Polysulfate compound prepared in Example 46 (Potassium salt)	3.9
Polysulfate compound prepared in Example 50 (Sodium salt)	3.9
Polysulfate compound prepared in Example 51 (Sodium salt)	3.9
Polysulfate compound prepared in Example 52 (Sodium salt)	3.9
Polysulfate compound prepared in Example 54 (Potassium salt)	1.95

(to be continued)

Test compound	HIV proliferation inhibitory action, 100% inhibition concentration (μg/ml)
Polysulfate compound prepared in Example 57 (Sodium salt)	3.9
Polysulfate compound prepared in Example 61 (Sodium salt)	1.95
Polysulfate compound prepared in Example 64 (Sodium salt)	3.9
Polysulfate compound prepared in Example 66 (Potassium salt)	0.98
Polysulfate compound prepared in Example 67 (Sodium salt)	0.98
Polysulfate compound prepared in Example 68 (Sodium salt)	1.95
Polysulfate compound prepared in Example 69 (Sodium salt)	1.95
Polysulfate compound prepared in Example 70 (Sodium salt)	3.90
Polysulfate compound prepared in Example 71 (Sodium salt)	1.95
Polysulfate compound prepared in Example 72 (Sodium salt)	1.95
Polysulfate compound prepared in Example 75 (Sodium salt)	3.9
Polysulfate compound prepared in Example 76 (Potassium salt)	3.9
Polysulfate compound prepared in Example 77 (Potassium salt)	1.95
Polysulfate compound prepared in Example 79 (Potassium salt)	3.8
Polysulfate compound prepared in Example 81 (Potassium salt)	3.9
Polysulfate compound prepared in Example 84 (Potassium salt)	0.98
Polysulfate compound prepared in Example 85 (Potassium salt)	1.95

(to be continued)

Test compound	HIV proliferation inhibitory action, 100% inhibition concentration (μg/ml)
Polysulfate compound prepared in Example 86 (Potassium salt)	1.50
Polysulfate compound prepared in Example 87 (Potassium salt)	1.95

(Effect of the Invention)

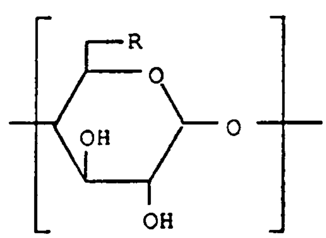
The polysulfate compound according to this invention is characterized by an excellent antiretrovirus action, particularly an excellent HIV proliferation inhibitory action as described above and further by low toxicity, proving high safety as pharmaceuticals.

The present polysulfate compound further shows only a low level of side effects such as anticoagulant action specific to sulfated polysaccharides.

Claims

Claims for the following Contracting States : DE, GB, FR, IT, NL, SE, CH, BE, AT, LU, DK

1. A polysulfate of a cyclodextrin in which at least one of 6 to 8 D-glucose units constituting the cyclodextrin has been replaced by a unit represented by Formula (1):



(I)

wherein R is a group represented by the formula:

1) $-OSO_2R^1$, 2) $-SR^2$,

3) $-\overset{R^3}{\overset{|}{N}}R^4$,

4) $-NHSO_2R^5$ or

5) $-\overset{R^7}{\overset{|}{N}}COR^6$;

where R^1 represents a mesityl group;

R^2 represents an C_{1-20} alkyl group; a C_{1-4} alkyl group having 1 to 3 substituents selected from

phenyl, a halogeno-substituted phenyl group and a C_{1-4} alkoxy-substituted phenyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a dihydroxy-substituted pyrimidinyl group or a purinyl group,

one of R^3 and R^4 represents a C_{1-4} alkyl group; a hydroxy-substituted C_{1-4} alkyl group; an amino-substituted C_{1-4} alkyl group; a C_{3-8} cycloalkyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a C_{1-4} alkoxy phenyl-substituted C_{1-4} alkyl group; a phenyl-substituted C_{1-4} alkyl group; and the other represents a hydrogen atom or a C_{1-4} alkyl group, or both may be combined at their ends to form a C_{1-4} alkylene group,

R^5 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a naphthyl group; a thienyl group; a C_{1-4} alkyl-substituted isooxazolyl group or a C_{1-4} alkyl-substituted thiazolyl group;

R^6 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from a hydroxy group, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a phenyl-substituted C_{1-4} alkyl group; a thienyl group; or a pyrenylcarbonyl-substituted C_{1-4} alkyl group; and

R^7 represents a hydrogen atom; or a C_{1-4} alkyl group substituted by a C_{2-5} alkanoylamino group or a benzoylamino group, or a salt thereof.

2. The compound according to claim 1, in which R is a group of the formula: $-OSO_2R^1$, and R^1 is a mesityl group.

3. The compound according to claim 1, in which R is a group of the formula: $-SR^2$, and R^2 is a C_{1-20} alkyl group; a C_{1-4} alkyl having 1 to 3 substituents selected from a phenyl group, a halogeno-substituted phenyl group and a C_{1-4} alkoxy-substituted phenyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a dihydroxy-substituted pyrimidinyl group or a purinyl group.

4. The compound according to claim 1, in which R is a group of the formula:

$$\begin{array}{c} R^3 \\ | \\ -NR^4, \end{array}$$

and one of R^3 and R^4 are a C_{1-4} alkyl group; a hydroxy-substituted C_{1-4} alkyl group; an amino-substituted C_{1-4} alkyl group; a C_{3-8} cycloalkyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4}alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a phenyl-substituted C_{1-4} alkyl group; a C_{1-4} alkoxyphenyl-substituted C1-4 alkyl group; and the other is a hydrogen atom or a C_{1-4} alkyl group;
or both may be combined at their ends to form a C_{1-4} alkylene group.

5. The compound according to claim 1, in which R is a group of the formula: $-NHSO_2R^{5,}$ and R5 is a C_{1-20} alkyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a naphthyl group; a thienyl group; a C_{1-4} alkyl-substituted isooxazolyl group or a C_{1-4} alkyl-substituted thiazolyl group.

6. The compound according to claim 1, in which R is a group of the formula:

$$\begin{array}{c} R^7 \\ | \\ -NCOR^6, \end{array}$$

and R^6 is C_{1-20} alkyl group; a phenyl group; a hydroxy-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a phenyl-substituted C_{1-4} alkyl group; a thienyl group or a pyrenylcarbonyl-substituted C_{1-4} alkyl group and R^7 is a hydrogen atom; a C_{2-5} alkanoylamino-substituted C_{1-4} alkyl group or a benzoylamino-substituted C_{1-4} alkyl group.

7. The compound according to Claim 3 or 6, which is a polysulfate of a α-cyclodextrin in which at least one of 6 D-glucose units has been replaced by a unit represented by Formula (I), or a salt thereof.

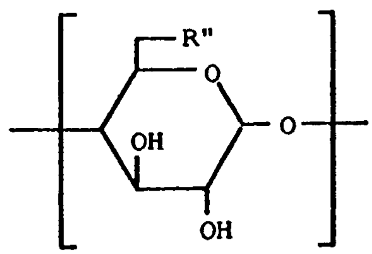
8. The compound according to any one of Claim 2 through 6, which is a polysulfate of a β-cycrodextrin in which at least one of 7 D-glucose units has been replaced by a unit represented by Formula (I), or a salt thereof.

9. The compound according to Claim 3, which is a polysulfate of a γ-cyclodextrin in which at least one of 8 D-glucose units has been replaced by a unit represented by Formula (I), or a salt thereof.

10. The compound according to claim 1, in which the number of the sulfate group in the molecule is 8 to 23.

11. The compound according to claim 1, in which R is a N-benzoyl-N-2-benzoylaminoethylamino group, an octadecanoylamino group, a hexanoylamino group, an octanoylamino group, a 1-pyrenylcarbonylpropanoylamino group, a 4-metoxyphenylamino group, a 2-naphthylsulfonyloxy group, an octylsulfonylamino group, a mesitylenesulfonyloxy group, a benzylthio group, a 4-chlorobenzylthio group, a 4-methoxybenzylthio group, a 4-methylphenylthio group, a 4-methoxyphenyl group or a purinylthio group.

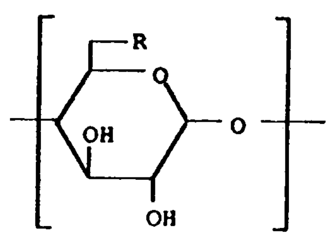
12. A polysulfate of a cyclodextrin as claimed in claim 2, wherein the cyclodextrin is a β-cyclodextrin and wherein 1 to 7-D-glucose units constituting β-cyclodextrin has been replaced by a unit represented by Formula (I) and wherein 0 to 2 D-glucose units has been replaced by a unit represented by Formula (V):



(V)

wherein R" is a pyridinio group or a lower-alkylamino group.

13. A process for preparing a polysulfate of a cyclodextrin in which at least one of 6 to 8 D-glucose units constituting the cyclodextrin has been replaced by a unit represented by Formula (I):



(I)

wherein R is a group represented by the formula:

1) OSO_2R^1, 2) $-SR^2$,

$$3)\ -\overset{R^3}{\overset{|}{N}}R^4,$$

4) $-NHSO_2R^5$ or

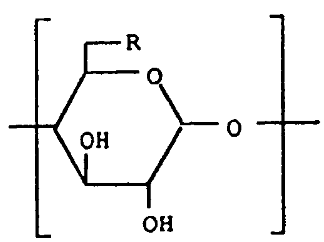
$$5)\ -\overset{R^7}{\overset{|}{N}}COR^6;$$

where R^1 represents mesityl group;
R^2 represents an C_{1-20} alkyl group; a C_{1-4} alkyl group having 1 to 3 substituents selected from a phenyl group, a halogeno-substituted phenyl group and a C_{1-4} alkoxy-substituted phenyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a dihydroxy-substituted pyrimidinyl group or a purinyl group;
one of R^3 and R^4 represents a C_{1-4} alkyl group; a hydroxy-substituted C_{1-4} alkyl group; an amino-substituted C_{1-4} alkyl group; a C_{3-8} cycloalkyl group; a phenyl group having substitutent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a C_{1-4} alkoxy phenyl-substituted C_{1-4} alkyl group; or a phenyl-substituted C_{1-4} alkyl group; and the other represents a hydrogen atom or a C_{1-4} alkyl group, or both may be combined at their ends to form a C_{1-4} alkylene group,
R^5 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a naphthyl group; a thienyl group; a C_{1-4} alkyl-substituted isooxazolyl group or a C_{1-4} alkyl-substituted thiazolyl group;
R^6 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from a hydroxy group, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a phenyl-substituted C_{1-4} alkyl group; a thienyl group; or a pyrenylcarbonyl-substituted C_{1-4} alkyl group; and
R^7 represents a hydrogen atom; or a C_{1-4} alkyl group substituted by a C_{2-5} alkanoylamino group or a benzoylamino group,
or a salt thereof,
which comprises reacting a cyclodextrin derivative in which at least one of 6 to 8 D-glucose units constituting the cyclodextrin is replaced by the unit or units represented by the Formula (I), with a sulfonating agent, and then converting the product into a salt, if desired.

14. A pharmaceutical composition which comprises a therapeutically effective amount of the compound claimed in any one of claims 1 to 12 and a pharmaceutically acceptable carrier therefor.

Claims for the following Contracting States : ES, GR

1. A process for preparing a pharmaceutical composition wherein a pharmaceutically acceptable carrier is admixed with a therapeutically effective amount of polysulfate of a cyclodextrin in which at least one of 6 to 8 D-glucose units constituting the cyclodextrin has been replaced by a unit represented by Formula(1):



(I)

wherein R is a group represented by the formula:

1) $-OSO_2R^1$, 2) $.-SR^2$,

$$3)\ -\overset{\overset{\large R^3}{|}}{N}R^4,$$

4) $-NHSO_2R^5$ or

$$5)\ -\overset{\overset{\large R^7}{|}}{N}COR^6;$$

where R^1 represents a mesityl group;
R^2 represents an C_{1-20} alkyl group; a C_{1-4} alkyl group having 1 to 3 substituents selected from phenyl, a halogeno-substituted phenyl group and a C_{1-4} alkoxy-substituted phenyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a dihydroxy-substituted pyrimidinyl group or a purinyl group,
one of R^3 and R^4 represents a C_{1-4} alkyl group; a hydroxy-substituted C_{1-4} alkyl group; an amino-substituted C_{1-4} alkyl group; a C_{3-8} cycloalkyl group; a phenyl group having substitutent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a C_{1-4} alkoxy phenyl-substituted C_{1-4} alkyl group; or a phenyl-substituted C_{1-4} alkyl group; and the other represents a hydrogen atom or a C_{1-4} alkyl group, or both may be combined at their ends to form a C_{1-4} alkylene group,
R^5 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a naphthyl group; a thienyl group; a C_{1-4} alkyl-substituted isooxazolyl group or a C_{1-4} alkyl-substituted thiazolyl group;
R^6 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from a hydroxy group, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a phenyl-substituted C_{1-4} alkyl group; a thienyl group; or a pyrenylcarbonyl-substituted C_{1-4} alkyl group; and
R^7 represents a hydrogen atom; or a C_{1-4} alkyl group substituted by a C_{2-5} alkanoylamino group or a benzoylamino group,
or a salt thereof.

2. A process according to claim 1, in which R is a group of the formula: $-OSO_2R^1$, and R^1 is a mesityl group.

3. A process according to claim 1, in which R is a group of the formula: $-SR^2$, and R^2 is a C_{1-20} alkyl group; a C_{1-4} alkyl having 1 to 3 substituents selected from a phenyl group, a halogeno-substituted phenyl group and a C_{1-4} alkoxy-substituted phenyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a dihydroxy-substituted pyrimidinyl group or a purinyl group.

4. A process according to claim 1, in which R is a group of the formula:

$$-\overset{\overset{\large R^3}{|}}{N}R^4,$$

and R^3 and R^4 are a C_{1-4} alkyl group; a hydroxy-substituted C_{1-4} alkyl group; an amino-substituted C_{1-4} alkyl group; a C_{3-8} cycloalkyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a phenyl-substituted C_{1-4} alkyl group; a C_{1-4} alkoxyphenyl-substituted C1-4 alkyl group; and the other is a hydrogen atom or a C_{1-4} alkyl group;
or both may be combined at their ends to form a C_{1-4} alkylene group.

5. A process according to claim 1, in which R is a group of the formula: $-NHSO_2R^{5}$, and R5 is a C_{1-20} alkyl group; a phenyl group; a halogeno-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a naphthyl group; a thienyl group; a C_{1-4} alkyl-substituted isooxazolyl group or a C_{1-4} alkyl-substituted thiazolyl group.

6. A process according to claim 1, in which R is a group of the formula:

$$\begin{array}{c} R^7 \\ | \\ -NCOR^6, \end{array}$$

and R^6 is C_{1-20} alkyl group; a phenyl gorup; a hydroxy-substituted phenyl group; a C_{1-4} alkyl-substituted phenyl group; a C_{1-4} alkoxy-substituted phenyl group; a phenyl-substituted C_{1-4} alkyl group; a thienyl group or a pyrenylcarbonyl-substituted C_{1-4} alkyl group and R^7 is a hydrogen atom; a C_{2-5} alkanoylamino-substituted C_{1-4} alkyl group or a benzoylamino-substituted C_{1-4} alkyl group.

7. A process according to claim 3 or 6, which is a polysulfate of a α-cyclodextrin in which at least one of 6 D-gulcose units has been replaced by a unit represented by Formula (I), or a salt thereof.

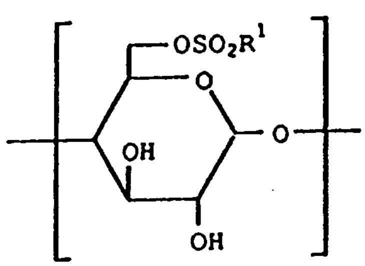
8. A process according to any one of claims 2 through 6, which is a polysulfate of a β-cycrodextrin in which at least one of 7 D-glucose units has been replaced by a unit represented by Formula (I), or a salt thereof.

9. A process according to Claim 3, which is a polysulfate of a γ-cycrodextrin in which at least one of 8 D-glucose units has been replaced by a unit represented by Formula (I), or a salt thereof.

10. A process according to claim 1, in which the number of the sulfate group in the molecule is 8 to 23.

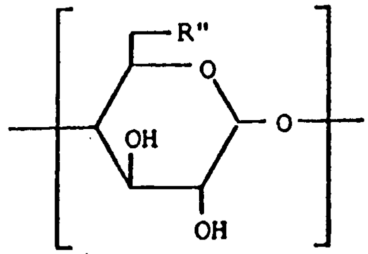
11. A process according to claim 1, in which R is a N-benzoyl-N-2-benzoylaminoethylamino group, an octadecanoylamino group, a hexanoylamino group, an octanoylamino group, a 1-pyrenylcarbonyl-propanoylamino group, a 4-metoxyphenylamino group, a 2-naphthylsulfonyloxy group, an octylsulfonylamino group, a mesitylenesulfonyloxy group, a benzylthio group, a 4-chlorobenzylthio group, a 4-methoxybenzylthio group, a 4-methylphenylthio group, a 4-methoxyphenyl group or a purinylthio group.

12. A process as claimed in claim 1 wherein the polysulphate is a sulfate of a β-cyclodextrin in which one to 7 D-glucose units constituting β-cyclodextrin has been replaced by a unit represented by Formula (IV):



(IV)

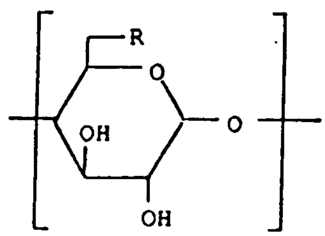
wherein R^1 is a mesityl group, and 0 to 2 D-glucose units has been replaced by a unit represented by Formula (V)



(V)

wherein R" is pyridinio group or a lower-alkylamino group.

13. A process for preparing a polysulfate of a cyclodextrin in which at least one of 6 to 8 D-glucose units constituting the cyclodextrin has been replaced by a unit represented by Formula(I):



(I)

wherein R is a group represented by the formula:

1) OSO_2R^1, 2) $-SR^2$,

3) $-\overset{R^3}{\overset{|}{N}}R^4$,

4) $-NHSO_2R^5$ or

5) $-\overset{R^7}{\overset{|}{N}}COR^6$;

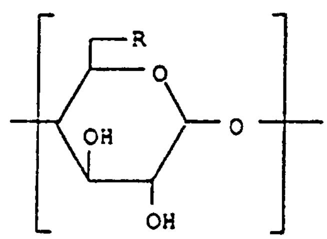
where R^1 represents mesityl group;
R^2 represents an C_{1-20} alkyl group; a C_{1-4} alkyl group having 1 to 3 substituents selected from a phenyl group, a halogeno-substituted phenyl group and a C_{1-4} alkoxy-substituted phenyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a dihydroxy-substituted pyrimidinyl group or a purinyl group,
one of R^3 and R^4 represents a C_{1-4} alkyl group; a hydroxy-substituted C_{1-4} alkyl group; an amino-substituted C_{1-4} alkyl group; a C_{3-8} cycloalkyl group; a phenyl group having substitutent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a C_{1-4} alkoxy phenyl-substituted C_{1-4} alkyl group; or a phenyl-substituted C_{1-4} alkyl group; and the other both may be combined at their ends to form a C_{1-4} alkylene group,
R^5 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from halogen, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a naphthyl group; a thienyl group; a C_{1-4} alkyl-substituted isooxazolyl group or a C_{1-4} alkyl-substituted thiazolyl group;
R^6 represents an C_{1-20} alkyl group; a phenyl group having substituent(s) selected from a hydroxy group, a C_{1-4} alkyl group and a C_{1-4} alkoxy group; a phenyl group; a phenyl-substituted C_{1-4} alkyl

group; a thienyl group; or a pyrenylcarbonyl-substituted C_{1-4} alkyl group; and
R^7 represents a hydrogen atom; or a C_{1-4} alkyl group substituted by a C_{2-5} alkanoylamino group or a benzoylamino group,
or a salt thereof,
which comprises reacting a cyclodextrin derivative in which at least one of 6 to 8 D-glucose units constituting the cyclodextrin is replaced by the unit or units represented by the Formula (I), with a sulfonating agent, and then converting the product into a salt, if desired.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : DE, GB, FR, IT, NL, SE, CH, BE, AT, LU, DK

1. Polysulfat eines Cyclodextrins, bei dem mindestens eine von 6 bis 8 D-Glucoseeinheiten, aus denen Cyclodextrin besteht, durch eine durch folgende Formel (I) dargestellte Einheit ersetzt ist:



(I)

worin R eine Gruppe ist, die durch die folgende Formel dargestellt wird:

1) $-OSO_2R^1$, 2) $-SR^2$, 3) $-NR^3R^4$, 4) $-NHSO_2R^5$ oder 5) $-NR^7COR^6$;

worin R^1 eine Mesitylgruppe darstellt;
R^2 eine C_{1-20}-Alkylgruppe, eine C_{1-4}-Alkylgruppe mit 1 bis 3 Substituenten, die unter Phenyl, einer Halogen-substituierten Phenylgruppe und einer C_{1-4}-Alkoxy-substituierten Phenylgruppe ausgewählt sind, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Dihydroxy-substituierte Pyrimidinylgruppe oder eine Purinylgruppe darstellt;
einer von R^3 und R^4 eine C_{1-4}-Alkylgruppe, eine Hydroxy-substituierte C_{1-4}-Alkylgruppe, eine Amino-substituierte C_{1-4}-Alkylgruppe, eine C_{3-8}-Cycloalkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkyoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine C_{1-4}-Alkoxyphenyl-substituierte C_{1-4}-Alkylgruppe oder eine Phenyl-substituierte C_{1-4}-Alkylgruppe darstellt und der andere ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe darstellt oder beide an ihren Enden unter Bildung einer C_{1-4}-Alkylengruppen verknüpft sind;
R^5 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkyoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Naphthylgruppe, eine Thienylgruppe, eine C_{1-4}-Alkyl-substituierte Isooxazolylgruppe oder eine C_{1-4}-Alkyl-substituierte Thiazolylgruppe darstellt;
R^6 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter einer Hyroxygruppe, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Phenyl-substituierte C_{1-4}-Alkylgruppe, eine Thienylgruppe oder eine Pyrenylcarbonyl-substituierte C_{1-4}-Alkylgruppe darstellt; und
R^7 ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe, die mit einer C_{2-5}-Alkanoylaminogruppe oder einer Benzoylaminogruppe substituiert ist;
oder ein Salz davon.

2. Verbindung nach Anspruch 1, bei der R eine Gruppe der Formel $-OSO_2R^1$ ist und R^1 eine Mesitylgruppe ist.

3. Verbindung nach Anspruch 1, bei der R eine Gruppe der Formel $-SR^2$ ist und R^2 eine C_{1-20}-Alkylgruppe, eine C_{1-4}-Alkylgruppe mit 1 bis 3 Substituenten, die unter Phenyl, einer Halogen-substituierten Phenylgruppe und einer C_{1-4}-Alkoxy-substituierten Phenylgruppe ausgewählt sind, eine Phenylgruppe, eine Halogen-substutuierte Phenylgruppe, eine C_{1-4}-Alkyl-substituierte Phenylgruppe, eine C_{1-4}-Alkoxy-substituierte Phenylgruppe, eine Dihydroxy-substituierte Pyrimidinylgruppe oder eine Purinylgruppe darstellt.

4. Verbindung nach Anspruch 1, bei der R eine Gruppe der Formel $-NR^3R^4$ ist und einer von R^3 und R^4 eine C_{1-4}-Alkylgruppe, eine Hydroxy-substituierte C_{1-4}-Alkylgruppe, eine Amino-substituierte C_{1-4}-Alkylgruppe, eine C_{3-8}-Cycloalkylgruppe, eine Phenylgruppe, eine Halogen-substituierte Phenylgruppe, eine C_{1-4}-Alkyl-substituierte Phenylgruppe, eine C_{1-4}-Alkyoxy-substituierte Phenylgruppe, eine Phenyl-substituierte C_{1-4}-Alkylgruppe, eine C_{1-4}-Alkoxyphenyl-substituierte C_{1-4}-Alkylgruppe darstellt und der andere ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe darstellt oder beide an ihren Enden unter Bildung eine C_{1-4}-Alkylengruppen verknüpft sind.

5. Verbindung nach Anspruch 1, bei der R eine Gruppe der Formel $-NHSO_2R^5$ ist und R^5 eine C_{1-20} Alkylgruppe, eine Phenylgruppe, eine Halogen-substituierte Phenylgruppe, eine C_{1-4}-Alkyl-substituierte Phenylgruppe, eine C_{1-4}-Alkyoxy-substituierte Phenylgruppe, eine Naphthylgruppe, eine Thienylgruppe, eine C_{1-4}-Alkyl-substituierte Isooxazolylgruppe oder eine eine C_{1-4}-Alkyl-substituierte Thiazolylgruppe darstellt.

6. Verbindung nach Anspruch 1, bei der R eine Gruppe der Formel $-NR^7COR^6$ ist und R^6 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe, eine Hydroxy-substituierte Phenylgruppe, eine C_{1-4}-Alkyl-substituierte Phenylgruppe, eine C_{1-4}-Alkyoxy-substituierte Phenylgruppe, eine Phenyl-substituierte C_{1-4}-Alkylgruppe, eine Thienylgruppe oder eine Pyrenylcarbonyl-substituierte C_{1-4}-Alkylgruppe darstellt und R^7 ein Wasserstoffatom, eine C_{2-5}-Alkanoylamino-substituierte C_{1-4}-Alkylgruppe oder eine Benzoylamino-substituierte C_{1-4}-Alkylgruppe darstellt.

7. Verbindung nach Anspruch 3 oder 6, die ein Polysulfat eines α-Cyclodextrins ist, bei dem mindestens eine von 6 D-Glucose-Einheiten durch eine durch die Formel (I) dargestellte Einheit ersetzt ist, oder ein Salz davon.

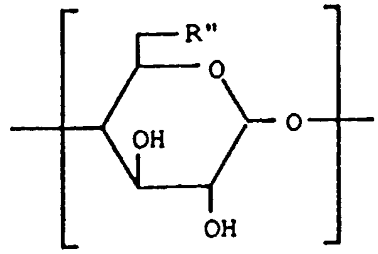
8. Verbindung nach einem der Ansprüche 2 bis 6, die ein Polysulfat eines β-Cyclodextrins ist, bei dem mindestens eine von 7 D-Glucose-Einheiten durch eine durch die Formel (I) dargestellte Einheit ersetzt ist, oder ein Salz davon.

9. Verbindung nach Anspruch 3, die ein Polysulfat eines γ-Cyclodextrins ist, bei dem mindestens eine von 8 D-Glucose-Einheiten durch eine durch die Formel (I) dargestellte Einheit ersetzt ist, oder ein Salz davon.

10. Verbindung nach Anspruch 1, bei der die Anzahl von Sulfatgruppen in dem Molekül 8 bis 23 ist.

11. Verbindung nach Anspruch 1, bei der R eine N-Benzoyl-N-2-benzoylaminoethylaminogruppe, eine Octadecanoylaminogruppe, eine Hexanoylaminogruppe, eine Octanoylaminogruppe, eine 1-Pyrenylcarbonylpropanoylaminogruppe, eine 4-Methoxyphenylaminogruppe, eine 2-Naphthylsulfonyloxygruppe, eine Octylsulfonylaminogruppe, eine Mesitylensulfonyloxygruppe, eine Benzylthiogruppe, eine 4-Chlorbenzylthiogruppe, eine 4-Methoxybenzylthiogruppe, eine 4-Methylphenylthiogruppe, eine 4-Methoxyphenylgruppe oder eine Purinylthiogruppe darstellt.

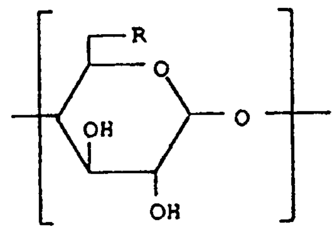
12. Polysulfat eines Cyclodextrins nach Anspruch 2, bei dem das Cyclodextrin ein β-Cyclodextrin ist und worin 1 bis 7 D-Glucoseeinheiten, aus denen β-Cyclodextrin besteht, durch eine durch folgende Formel (I) dargestellte Einheit ersetzt ist/sind und worin 0 bis 2 D-Glucose-Einheiten durch eine durch die Formel (V) dargestellte Einheit ersetzt ist/sind:



(V)

worin R" eine Pyridingruppe oder eine niedere Alkylaminogruppe darstellt.

13. Verfahren zur Herstellung eines Polysulfats eines Cyclodextrins, bei dem mindestens einer von 6 bis 8 D-Glucose-Einheiten, aus dem Cyclodextrin besteht, durch eine durch die folgende Formel (I) dargestellte Einheit ersetzt ist:



(I)

worin R eine Gruppe ist, die durch die folgende Formel dargestellt wird:

1) $-OSO_2R^1$, 2) $-SR^2$, 3) $-NR^3R^4$, 4) $-NHSO_2R^5$ oder 5) $-NR^7COR^6$;

worin R^1 eine Mesitylgruppe darstellt;

R^2 eine C_{1-20}-Alkylgruppe, eine C_{1-4}-Alkylgruppe mit 1 bis 3 Substituenten, die unter Phenyl, einer Halogen-substituierten Phenylgruppe und einer C_{1-4}-Alkoxy-substituierten Phenylgruppe ausgewählt sind, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Dihydroxy-substituierte Pyrimidinylgruppe oder eine Purinylgruppe darstellt;

einer von R^3 und R^4 eine C_{1-4}-Alkylgruppe, eine Hydroxy-substituierte C_{1-4}-Alkylgruppe, eine Amino-substituierte C_{1-4}-Alkylgruppe, eine C_{3-8}-Cycloalkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkyoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine C_{1-4}-Alkoxyphenyl-substituierte C_{1-4}-Alkylgruppe oder eine Phenyl-substituierte C_{1-4}-Alkylgruppe darstellt und der andere ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe darstellt oder beide an ihren Enden unter Bildung einer C_{1-4}-Alkylengruppen verknüpft sind;

R^5 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkyoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Naphthylgruppe, eine Thienylgruppe, eine C_{1-4}-Alkyl-substituierte Isooxazolylgruppe oder eine C_{1-4}-Alkyl-substituierte Thiazolylgruppe darstellt;

R^6 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter einer Hyroxygruppe, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Phenyl-substituierte C_{1-4}-Alkylgruppe, eine Thienylgruppe oder eine Pyrenylcarbonyl-substituierte C_{1-4}-Alkylgruppe darstellt; und

R^7 ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe, die mit einer C_{2-5}-Alkanoylaminogruppe oder einer Benzoylaminogruppe substituiert ist, darstellt;

oder eines Salzes davon,

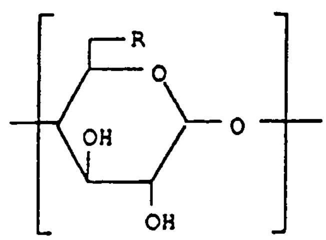
welches umfaßt, Umsetzen eines Cyclodextrin-Derivats, bei dem mindestens eine von 6 bis 8 D-Glucose-Einheiten, aus denen das Cyclodextrin besteht, durch eine (mehrere) durch die Formel (I)

dargestellte Einheit(en) ersetzt ist mit einem Sulfonierungsmittel und anschließend, wenn gewünscht, Umwandeln des Produkts in ein Salz.

14. Arzneimittelzusammensetzung, welche eine therapeutisch wirksame Menge der Verbindung nach einem der Ansprüche 1 bis 12 und einen pharmazeutisch verträglichen Träger dafür umfaßt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Arzneimittelzusammensetzung, bei der ein pharmazeutisch verträglicher Träger vermischt wird mit einer pharmazeutisch wirksamen Menge eines Polysulfats eines Cyclodextrins, bei dem mindestens eine von 6 bis 8 D-Glucoseeinheiten, aus denen Cyclodextrin besteht, durch eine durch folgende Formel (I) dargestellte Einheit ersetzt ist:



(I)

worin R eine Gruppe ist, die durch die folgende Formel dargestellt wird:

1) $-OSO_2R^1$, 2) $-SR^2$, 3) $-NR^3R^4$, 4) $-NHSO_2R^5$ oder 5) $-NR^7COR^6$;

worin R^1 eine Mesitylgruppe darstellt;

R^2 eine C_{1-20}-Alkylgruppe, eine C_{1-4}-Alkylgruppe mit 1 bis 3 Substituenten, die unter Phenyl, einer Halogen-substituierten Phenylgruppe und einer C_{1-4}-Alkoxy-substituierten Phenylgruppe ausgewählt sind, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Dihydroxy-substituierte Pyrimidinylgruppe oder eine Purinylgruppe darstellt;

einer von R^3 und R^4 eine C_{1-4}-Alkylgruppe, eine Hydroxy-substituierte C_{1-4}-Alkylgruppe, eine Amino-substituierte C_{1-4}-Alkylgruppe, eine C_{3-8}-Cycloalkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkyoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine C_{1-4}-Alkoxyphenyl-substituierte C_{1-4}-Alkylgruppe oder eine Phenyl-substituierte C_{1-4}-Alkylgruppe darstellt und der andere ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe darstellt oder beide an ihren Enden unter Bildung einer C_{1-4}-Alkylengruppen verknüpft sind;

R^5 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkyoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Naphthylgruppe, eine Thienylgruppe, eine C_{1-4}-Alkyl-substituierte Isooxazolylgruppe oder eine C_{1-4}-Alkyl-substituierte Thiazolylgruppe darstellt;

R^6 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter einer Hyroxygruppe, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Phenyl-substituierte C_{1-4}-Alkylgruppe, eine Thienylgruppe oder eine Pyrenylcarbonyl-substituierte C_{1-4}-Alkylgruppe darstellt; und

R^7 ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe, die mit einer C_{2-5}-Alkanoylaminogruppe oder einer Benzoylaminogruppe substituiert ist;

oder einem Salz davon.

2. Verfahren nach Anspruch 1, wobei R eine Gruppe der Formel $-OSO_2R^1$ ist und R^1 eine Mesitylgruppe darstellt.

3. Verfahren nach Anspruch 1, wobei R eine Gruppe der Formel $-SR^2$ ist, und R^2 eine C_{1-20}-Alkylgruppe, eine C_{1-4}-Alkylgruppe mit 1 bis 3 Substituenten, die unter Phenyl, einer Halogen-substituierten

Phenylgruppe und einer C_{1-4}-Alkoxy-substituierten Phenylgruppe ausgewählt sind, eine Phenylgruppe, eine Halogen-substutuierte Phenylgruppe, eine C_{1-4}-Alkyl-substituierte Phenylgruppe, eine C_{1-4}-Alkoxy-substituierte Phenylgruppe, eine Dihydroxy-substituierte Pyrimidinylgruppe oder eine Purinylgruppe darstellt.

4. Verfahren nach Anspruch 1, wobei R eine Gruppe der Formel $-NR^3R^4$ ist und einer von R^3 und R^4 eine C_{1-4}-Alkylgruppe, eine Hydroxy-substituierte C_{1-4}-Alkylgruppe, eine Amino-substituierte C_{1-4}-Alkylgruppe, eine C_{3-8}-Cycloalkylgruppe, eine Phenylgruppe, eine Halogen-substituierte Phenylgruppe, eine C_{1-4}-Alkyl-substituierte Phenylgruppe, eine C_{1-4}-Alkyoxy-substituierte Phenylgruppe, eine Phenyl-substituierte C_{1-4}-Alkylgruppe, eine C_{1-4}-Alkoxyphenyl-substituierte C_{1-4}-Alkylgruppe darstellt und der andere ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe darstellt oder beide an ihren Enden unter Bildung eine C_{1-4}-Alkylengruppen verknüpft sind.

5. Verfahren nach Anspruch 1, wobei R eine Gruppe der Formel $-NHSO_2R^5$ ist und R^5 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe, eine Halogen-substituierte Phenylgruppe, eine C_{1-4}-Alkyl-substituierte Phenylgruppe, eine C_{1-4}-Alkyoxy-substituierte Phenylgruppe, eine Naphthylgruppe, eine Thienylgruppe, eine C_{1-4}-Alkyl-substituierte Isooxazolylgruppe oder eine eine C_{1-4}-Alkyl-substituierte Thiazolylgruppe darstellt.

6. Verfahren nach Anspruch 1, wobei R eine Gruppe der Formel $-NR^7COR^6$ ist und R^6 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe, eine Hydroxy-substituierte Phenylgruppe, eine C_{1-4}-Alkyl-substituierte Phenylgruppe, eine C_{1-4}-Alkyoxy-substituierte Phenylgruppe, eine Phenyl-substituierte C_{1-4}-Alkylgruppe, eine Thienylgruppe oder eine Pyrenylcarbonyl-substituierte C_{1-4}-Alkylgruppe darstellt und R^7 ein Wasserstoffatom, eine C_{2-5}-Alkanoylamino-substituierte C_{1-4}-Alkylgruppe oder eine Benzoylamino-substituierte C_{1-4}-Alkylgruppe darstellt.

7. Verfahren nach Anspruch 3 oder 6, wobei das Polysulfat ein Poylsulfat eines α-Cyclodextrins ist, bei dem mindestens eine von 6 D-Glucose-Einheiten durch eine durch die Formel (I) dargestellte Einheit ersetzt ist, oder ein Salz davon.

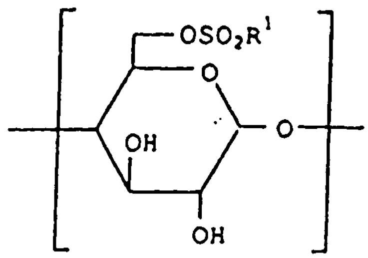
8. Verfahren nach einem der Ansprüche 2 bis 6, wobei das Poylsulfat ein Polysulfat eines β-Cyclodextrins ist, bei dem mindestens eine von 7 D-Glucose-Einheiten durch eine durch die Formel (I) dargestellte Einheit ersetzt ist, oder ein Salz davon.

9. Verfahren nach Anspruch 3, wobei das Polysulfat ein Polysulfat eines γ-Cyclodextrins ist, bei dem mindestens eine von 8 D-Glucose-Einheiten durch eine durch die Formel (I) dargestellte Einheit ersetzt ist, oder ein Salz davon.

10. Verfahren nach Anspruch 1, wobei die Anzahl von Sulfatgruppen in dem Molekül 8 bis 23 ist.

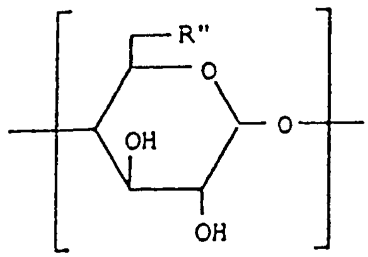
11. Verfahren nach Anspruch 1, wobei R eine N-Benzoyl-N-2-benzoylaminoethylaminogruppe, eine Octadecanoylaminogruppe, eine Hexanoylaminogruppe, eine Octanoylaminogruppe, eine 1-Pyrenylcarbonylpropanoylaminogruppe, eine 4-Methoxyphenylaminogruppe, eine 2-Naphthylsulfonyloxygruppe, eine Octylsulfonylaminogruppe, eine Mesitylensulfonyloxygruppe, eine Benzylthiogruppe, eine 4-Chlorbenzylthiogruppe, eine 4-Methoxybenzylthiogruppe, eine 4-Methylphenylthiogruppe, eine 4-Methoxyphenylgruppe oder eine Purinylthiogruppe darstellt.

12. Verfahren nach Anspruch 1, wobei das Polysulfat ein Polysulfat eines β-Cyclodextrins ist, worin 1 bis 7 D-Glucose-Einheit(en), aus denen β-Cyclodextrin besteht, durch eine durch folgende Formel (IV) dargestellte Einheit ersetzt ist (sind):



(IV)

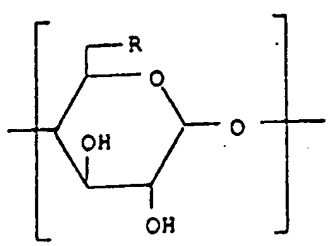
worin R^1 eine Mesitylgruppe darstellt und 0 bis 2 D-Glucose-Einheiten durch eine durch die folgende Formel (V) dargestellte Einheit ersetzt sind:



(V)

worin R" eine Pyridingruppe oder eine niedere Alkylaminogruppe ist.

13. Verfahren zur Herstellung eines Polysulfats eines Cyclodextrins, bei dem mindestens eine von 6 bis 8 D-Glucose-Einheiten, aus dem Cyclodextrin besteht, durch eine durch die folgende Formel (I) dargestellte Einheit ersetzt ist:



(I)

worin R eine Gruppe ist, die durch die folgende Formel dargestellt wird:

1) $-OSO_2R^1$, 2) $-SR^2$, 3) $-NR^3R^4$, 4) $-NHSO_2R^5$ oder 5) $-NR^7COR^6$;

worin R^1 eine Mesitylgruppe darstellt;

R^2 eine C_{1-20}-Alkylgruppe, eine C_{1-4}-Alkylgruppe mit 1 bis 3 Substituenten, die unter Phenyl, einer Halogen-substituierten Phenylgruppe und einer C_{1-4}-Alkoxy-substituierten Phenylgruppe ausgewählt sind, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Dihydroxy-substituierte Pyrimidinylgruppe oder eine Purinylgruppe darstellt;

einer von R^3 und R^4 eine C_{1-4}-Alkylgruppe, eine Hydroxy-substituierte C_{1-4}-Alkylgruppe, eine Amino-substituierte C_{1-4}-Alkylgruppe, eine C_{3-8}-Cycloalkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkyoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine C_{1-4}-Alkoxyphenyl-substituierte C_{1-4}-Alkylgruppe oder eine Phenyl-substituierte C_{1-4}-Alkylgruppe darstellt und der andere ein Wasserstoffatom oder eine C_{1-4}-

Alkylgruppe darstellt oder beide an ihren Enden unter Bildung einer C_{1-4}-Alkylengruppen verknüpft sind;

R^5 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter Halogen, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkyoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Naphthylgruppe, eine Thienylgruppe, eine C_{1-4}-Alkyl-substituierte Isooxazolylgruppe oder eine C_{1-4}-Alkyl-substituierte Thiazolylgruppe darstellt;

R^6 eine C_{1-20}-Alkylgruppe, eine Phenylgruppe mit (einem) Substituenten, (der) die unter einer Hyroxygruppe, einer C_{1-4}-Alkylgruppe und einer C_{1-4}-Alkoxygruppe ausgewählt (ist) sind, eine Phenylgruppe, eine Phenyl-substituierte C_{1-4}-Alkylgruppe, eine Thienylgruppe oder eine Pyrenylcarbonyl-substituierte C_{1-4}-Alkylgruppe darstellt; und

R^7 ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe, die mit einer C_{2-5}-Alkanoylaminogruppe oder einer Benzoylaminogruppe substituiert ist;

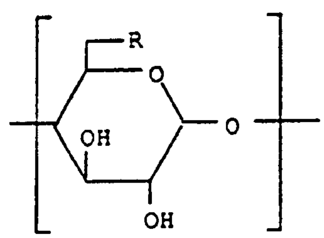
oder eines Salzes davon,

welches umfaßt, Umsetzen eines Cyclodextrin-Derivats, bei dem mindestens eine von 6 bis 8 D-Glucose-Einheiten, aus denen das Cyclodextrin besteht, durch eine (mehrere) durch die Formel (I) dargestellte Einheit(en) ersetzt ist mit einem Sulfonierungsmittel und anschließend, wenn gewünscht, Umwandeln des Produkts in ein Salz.

Revendications

Revendications pour les Etats contractants suivants : DE, GB, FR, IT, NL, SE, CH, BE, AT, LU, DK

1. Polysulfate d'une cyclodextrine, où au moins l'une des 6 à 8 unités D-glucose constituant la cyclodextrine a été remplacée par une unité représentée par la formule (I) :



(I)

dans laquelle R est un radical représenté par la formule :

1) $-OSO_2R^1$, 2) $-SR^2$,

3) $-\overset{\displaystyle R^3}{\overset{|}{N}}R^4$,

4) $-NHSO_2R^5$ ou

5) $-\overset{\displaystyle R^7}{\overset{|}{N}}COR^6$

où

R^1 représente le radical mésityle;

R^2 représente un radical alkyle en C_1-C_{20}, un radical alkyle en C_1-C_4 possédant de 1 à 3 substituants choisis parmi les radicaux phényle, phényle à substitution halogénée et phényle à substitution alcoxylique en C_1-C_4, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical

dihydroxy-pyrimidinyle, ou un radical purinyle;

l'un des symboles R^3 et R^4 représente un radical alkyle en C_1-C_4, un radical hydroxy-alkyle en C_1-C_4, un radical amino-alkyle en C_1-C_4, un radical cycloalkyle en C_3-C_8, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical alkyle en C_1-C_4 à substitution alcoxy(C_1-C_4), un radical alkyle en C_1-C_4 à substitution phénylique, cependant que l'autre de ces symboles représente un atome d'hydrogène ou un radical alkyle en C_1-C_4, ou bien ces deux symboles peuvent être combinés à leurs extrémités pour former un radical alkylène en C_1-C_4;

R^5 représente un radical alkyle en C_1-C_{20}, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, le radical naphtyle, le radical thiényle, un radical isooxazolyle à substitution alkylique en C_1-C_4, ou un radical thiazolyle à substitution alkylique en C_1-C_4;

R^6 représente un radical alkyle en C_1-C_{20}, un radical phényle possédant un ou plusieurs substituants choisis parmi les radicaux hydroxyle, alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical alkyle en C_1-C_4 à substitution phénylique, le radical thiényle, ou un radical alkyle en C_1-C_4 à substitution pyrénylcarbonylique, et

R^7 représente un atome d'hydrogène, ou un radical alkyle en C_1-C_4 substitué par un radical alcanoylamino en C_2-C_5, ou un radical benzoylamino,

ou un sel de celui-ci.

2. Composé suivant la revendication 1, dans lequel R représente un radical de la formule :

$-OSO_2R^1$

et R^1 représente le radical mésityle.

3. Composé suivant la revendication 1, dans lequel R représente le radical de la formule :

$-SR^2$

et R^2 représente un radical alkyle en C_1-C_{20}, un radical alkyle en C_1-C_4 comportant de 1 à 3 substituants choisis parmi les radicaux phényle, phényle à substitution halogénée et phényle à substitution alcoxylique en C_1-C_4, le radical phényle, un radical phényle à substitution halogénée, un radical phényle à substitution alkylique en C_1-C_4, un radical phényle à substitution alcoxylique en C_1-C_4, un radical dihydroxy-pyrimidinyle, ou un radical purinyle.

4. Composé suivant la revendication 1, caractérisé en ce que R représente un radical de la formule :

$$\begin{array}{c} R^3 \\ | \\ -NR^4 \end{array}$$

et l'un des symboles R^3 et R^4 représente un radical alkyle en C_1-C_4, un radical hydroxyalkyle en C_1-C_4, un radical aminoalkyle en C_1-C_4, un radical cycloalkyle en C_3-C_8, le radical phényle, un radical phényle à substitution halogénée, un radical phényle à substitution alkylique en C_1-C_4, un radical phényle à substitution alcoxylique en C_1-C_4, un radical alkyle en C_1-C_4 à substitution phénylique, un radical alkyle en C_1-C_4 à substitution alcoxy(C_1-C_4)phénylique, cependant que l'autre représente un atome d'hydrogène ou un radical alkyle en C_1-C_4, ou bien ces deux symboles peuvent être combinés à leurs extrémités pour former un radical alkylène en C_1-C_4.

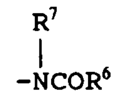
5. Composé suivant la revendication 1, dans lequel R représente le radical de la formule :

$-NHSO_2R^5$

et R^5 représente un radical alkyle en C_1-C_{20}, le radical phényle, un radical phényle à substitution halogénée, un radical phényle à substitution alkylique en C_1-C_4, un radical phényle à substitution

alcoxylique en C_1-C_4, le radical naphtyle, le radical thiényle, un radical isooxazolyle à substitution alkylique en C_1-C_4, ou un radical thiazolyle à substitution alkylique en C_1-C_4.

6. Composé suivant la revendication 1, dans lequel R représente un radical de la formule :



et R^6 représente un radical alkyle en C_1-C_{20}, le radical phényle, un radical hydroxyphényle, un radical phényle à substitution alkylique en C_1-C_4, un radical phényle à substitution alcoxylique en C_1-C_4, un radical alkyle en C_1-C_4 à substitution phénylique, un radical thiényle, ou un radical alkyle en C_1-C_4 à substitution pyrénylcarbonylique et R^7 représente un atome d'hydrogène, un radical alkyle en C_1-C_4 à substitution alcanoyl (C_2-C_5) amino, ou un radical alkyle en C_1-C_4 à substitution benzoylamino.

7. Composé suivant la revendication 3 ou 6, qui est un polysulfate d'une α-cyclodextrine, dans laquelle au moins l'une des 6 unités D-glucose a été remplacée par une unité représentée par la formule (I), ou un sel de celui-ci.

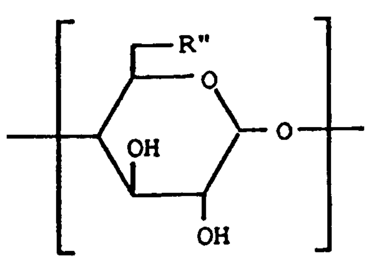
8. Composé suivant la revendication 2 à 6, qui est un polysulfate d'une β-cyclodextrine, dans laquelle au moins l'une des 7 unités D-glucose a été remplacée par une unité représentée par la formule (I), ou un sel de celui-ci.

9. Composé suivant la revendication 3, qui est un polysulfate d'une γ-cyclodextrine, dans laquelle au moins l'une des 8 unités D-glucose a été remplacée par une unité représentée par la formule (I), ou un sel de celui-ci.

10. Composé suivant la revendication 1, dans lequel le nombre des radicaux sulfate dans la molécule fluctue de 8 à 23.

11. Composé suivant la revendication 1, dans lequel R représente un radical N-benzoyl-N-2-benzoylaminoéthylamino, un radical octadécanoylamino, un radical hexanoylamino, un radical octanoylamino, un radical 1-pyrénylcarbonylpropanoylamino, un radical 4-méthoxyphénylamino, un radical 2-naphtylsulfonyloxy, un radical octylsulfonylamino, un radical mésitylènesulfonyloxy, un radical benzylthio, un radical 4-chlorobenzylthio, un radical 4-méthoxybenzylthio, un radical 4-méthylphénylthio, un radical 4-méthoxyphényle ou un radical purinylthio.

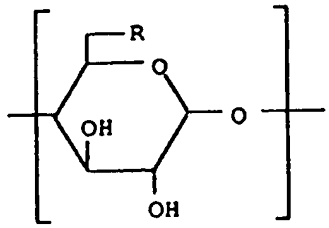
12. Polysulfate d'une cyclodextrine suivant la revendication 2, où la cyclodextrine est une β-cyclodextrine et où 1 à 7 unités D-glucose constituant la β-cyclodextrine ont été remplacées par une unité représentée par la formule (I) et où 0 à 2 unités D-glucose ont été remplacées par une unité représentée par la formule (V) :



(V)

dans laquelle R" représente le radical pyridinio ou un radical alkylamino inférieur.

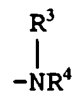
13. Procédé de préparation d'un polysulfate d'une cyclodextrine, où au moins l'une des 6 à 8 unités D-glucose constituant la cyclodextrine a été remplacée par une unité représentée par la formule (I) :



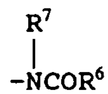
(I)

dans laquelle R est un radical représenté par la formule :

1) $-OSO_2R^1$, 2) $-SR^2$,

3) 

4) $-NHSO_2R^5$ ou

5) 

où

R^1 représente le radical mésityle;

R^2 représente un radical alkyle en C_1-C_{20}, un radical alkyle en C_1-C_4 possédant de 1 à 3 substituants choisis parmi les radicaux phényle, phényle à substitution halogénée et phényle à substitution alcoxylique en C_1-C_4, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical dihydroxy-pyrimidinyle, ou un radical purinyle;

l'un des symboles R^3 et R^4 représente un radical alkyle en C_1-C_4, un radical hydroxy-alkyle en C_1-C_4, un radical amino-alkyle en C_1-C_4, un radical cycloalkyle en C_3-C_8, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical alkyle en C_1-C_4 à substitution alcoxy(C_1-C_4), un radical alkyle en C_1-C_4 à substitution phénylique, cependant que l'autre de ces symboles représente un atome d'hydrogène ou un radical alkyle en C_1-C_4, ou bien ces deux symboles peuvent être combinés à leurs extrémités pour former un radical alkylène en C_1-C_4;

R^5 représente un radical alkyle en C_1-C_{20}, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, le radical naphtyle, le radical thiényle, un radical isooxazolyle à substitution alkylique en C_1-C_4, ou un radical thiazolyle à substitution alkylique en C_1-C_4;

R^6 représente un radical alkyle en C_1-C_{20}, un radical phényle possédant un ou plusieurs substituants choisis parmi les radicaux hydroxyle, alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical alkyle en C_1-C_4 à substitution phénylique, le radical thiényle, ou un radical alkyle en C_1-C_4 à substitution pyrénylcarbonylique, et

R^7 représente un atome d'hydrogène, ou un radical alkyle en C_1-C_4 substitué par un radical alcanoylamino en C_2-C_5, ou un radical benzoylamino,

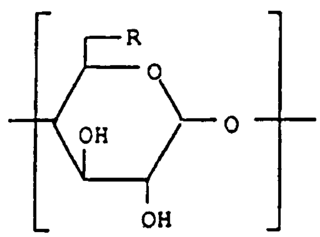
ou d'un sel de celui-ci,

caractérisé en ce que l'on fait réagir un dérivé de cyclodextrine, dans lequel au moins l'une des 6 à 8 unités D-glucose constituant la cyclodextrine a été remplacée par l'unité ou des unités représentées par la formule (I) avec un agent de sulfonation et on convertit ensuite le produit en un sel, si cela se révèle souhaitable.

14. Composition pharmaceutique, caractérisée en ce qu'elle comprend une proportion thérapeutiquement efficace du composé suivant l'une quelconque des revendications 1 à 12 et un véhicule ou excipient pharmaceutiquement acceptable pour ce composé.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'une composition pharmaceutique, conformément auquel on mélange un véhicule ou excipient pharmaceutiquement acceptable et une proportion thérapeutiquement efficace d'un polysulfate d'une cyclodextrine, où au moins l'une des 6 à 8 unités D-glucose constituant la cyclodextrine a été remplacée par une unité représentée par la formule (I) :



(I)

dans laquelle R est un radical représenté par la formule :

1) $-OSO_2R^1$, 2) $-SR^2$,

3) $-\underset{}{N}(R^3)R^4$,

4) $-NHSO_2R^5$ ou

5) $-N(R^7)COR^6$

où

R^1 représente le radical mésityle;

R^2 représente un radical alkyle en C_1-C_{20}, un radical alkyle en C_1-C_4 possédant de 1 à 3 substituants choisis parmi les radicaux phényle, phényle à substitution halogénée et phényle à substitution alcoxylique en C_1-C_4, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical dihydroxy-pyrimidinyle, ou un radical purinyle;

l'un des symboles R^3 et R^4 représente un radical alkyle en C_1-C_4, un radical hydroxy-alkyle en C_1-C_4, un radical amino-alkyle en C_1-C_4, un radical cycloalkyle en C_3-C_8, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical alkyle en C_1-C_4 à substitution alcoxy (C_1-C_4), un radical alkyle en C_1-C_4 à substitution phénylique, cependant que l'autre de ces symboles représente un atome d'hydrogène ou un radical alkyle en C_1-C_4, ou bien ces deux symboles peuvent être combinés à leurs extrémités pour former un radical alkylène en C_1-C_4;

R^5 représente un radical alkyle en C_1-C_{20}, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, le radical naphtyle, le radical thiényle, un radical isooxazolyle à substitution alkylique en C_1-C_4, ou un radical thiazolyle à substitution alkylique en C_1-C_4;

R^6 représente un radical alkyle en C_1-C_{20}, un radical phényle possédant un ou plusieurs substituants choisis parmi les radicaux hydroxyle, alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical

phényle, un radical alkyle en C_1-C_4 à substitution phénylique, le radical thiényle, ou un radical alkyle en C_1-C_4 à substitution pyrénylcarbonylique, et

R^7 représente un atome d'hydrogène, ou un radical alkyle en C_1-C_4 substitué par un radical alcanoylamino en C_2-C_5, ou un radical benzoylamino,

ou d'un sel de celui-ci.

2. Procédé suivant la revendication 1, dans lequel R représente un radical de la formule :

$-OSO_2R^1$

et R^1 représente le radical mésityle.

3. Procédé suivant la revendication 1, dans lequel R représente le radical de la formule :

$-SR^2$

et R^2 représente un radical alkyle en C_1-C_{20}, un radical alkyle en C_1-C_4 comportant de 1 à 3 substituants choisis parmi les radicaux phényle, phényle à substitution halogénée et phényle à substitution alcoxylique en C_1-C_4, le radical phényle, un radical phényle à substitution halogénée, un radical phényle à substitution alkylique en C_1-C_4, un radical phényle à substitution alcoxylique en C_1-C_4, un radical dihydroxy-pyrimidinyle, ou un radical purinyle.

4. Procédé suivant la revendication 1, caractérisé en ce que R représente un radical de la formule :

$$\begin{array}{c} R^3 \\ | \\ -NR^4 \end{array}$$

et l'un des symboles R^3 et R^4 représente un radical alkyle en C_1-C_4, un radical hydroxyalkyle en C_1-C_4, un radical aminoalkyle en C_1-C_4, un radical cycloalkyle en C_3-C_8, le radical phényle, un radical phényle à substitution halogénée, un radical phényle à substitution alkylique en C_1-C_4, un radical phényle à substitution alcoxylique en C_1-C_4, un radical alkyle en C_1-C_4 à substitution phénylique, un radical alkyle en C_1-C_4 à substitution alcoxy-(C_1-C_4)phénylique, cependant que l'autre représente un atome d'hydrogène ou un radical alkyle en C_1-C_4, ou bien ces deux symboles peuvent être combinés à leurs extrémités pour former un radical alkylène en C_1-C_4.

5. Procédé suivant la revendication 1, dans lequel R représente le radical de la formule :

$-NHSO_2R^5$

et R^5 représente un radical alkyle en C_1-C_{20}, le radical phényle, un radical phényle à substitution halogénée, un radical phényle à substitution alkylique en C_1-C_4, un radical phényle à substitution alcoxylique en C_1-C_4, le radical naphtyle, le radical thiényle, un radical isooxazolyle à substitution alkylique en C_1-C_4, ou un radical thiazolyle à substitution alkylique en C_1-C_4.

6. Procédé suivant la revendication 1, dans lequel R représente un radical de la formule :

$$\begin{array}{l} R^7 \\ | \\ -NCOR^6 \end{array}$$

et R^6 représente un radical alkyle en C_1-C_{20}, le radical phényle, un radical hydroxyphényle, un radical phényle à substitution alkylique en C_1-C_4, un radical phényle à substitution alcoxylique en C_1-C_4, un radical alkyle en C_1-C_4 à substitution phénylique, un radical thiényle, ou un radical alkyle en C_1-C_4 à

substitution pyrénylcarbonylique et R^7 représente un atome d'hydrogène, un radical alkyle en C_1-C_4 à substitution alcanoyl(C_2-C_5)amino, ou un radical alkyle en C_1-C_4 à substitution benzoylamino.

7. Procédé suivant la revendication 3 ou 6, qui est un polysulfate d'une α-cyclodextrine, dans laquelle au moins l'une des 6 unités D-glucose a été remplacée par une unité représentée par la formule (I), ou un sel de celui-ci.

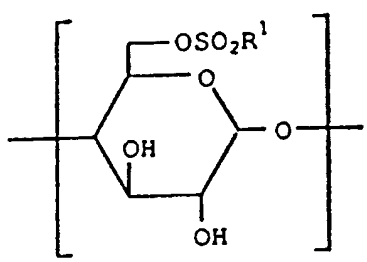
8. Procédé suivant la revendication 2 à 6, qui est un polysulfate d'une β-cyclodextrine, dans laquelle au moins l'une des 7 unités D-glucose a été remplacée par une unité représentée par la formule (I), ou un sel de celui-ci.

9. Procédé suivant la revendication 3, qui est un polysulfate d'une γ-cyclodextrine, dans laquelle au moins l'une des 8 unités D-glucose a été remplacée par une unité représentée par la formule (I), ou un sel de celui-ci.

10. Procédé suivant la revendication 1, dans lequel le nombre des radicaux sulfate dans la molécule fluctue de 8 à 23.

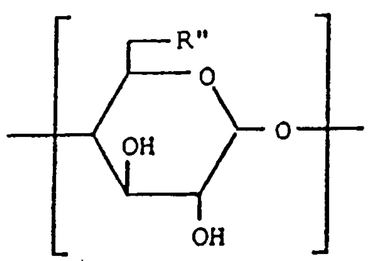
11. Procédé suivant la revendication 1, dans lequel R représente un radical N-benzoyl-N-2-benzoylaminoéthylamino, un radical octadécanoylamino, un radical hexanoylamino, un radical octanoylamino, un radical 1-pyrénylcarbonylpropanoylamino, un radical 4-méthoxyphénylamino, un radical 2-naphtylsulfonyloxy, un radical octylsulfonylamino, un radical mésitylènesulfonyloxy, un radical benzylthio, un radical 4-chlorobenzylthio, un radical 4-méthoxybenzylthio, un radical 4-méthylphénylthio, un radical 4-méthoxyphényle ou un radical purinylthio.

12. Procédé suivant la revendication 1, caractérisé en ce que le polysulfate est un sulfate de β-cyclodextrine, dans lequel 1 à 7 unités D-glucose constituant la β-cyclodextrine ont été remplacées par une unité représentée par la formule (IV) :



(IV)

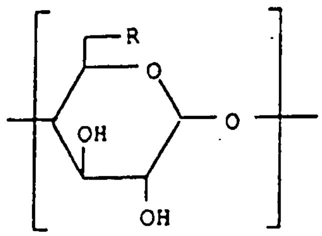
dans laquelle R^1 représente un radical mésityle et 0 à 2 unités D-glucose ont été remplacées par une unité représentée par la formule (V) :



(V)

dans laquelle R" représente le radical pyridinio ou un radical alkylamino inférieur.

13. Procédé de préparation d'un polysulfate d'une cyclodextrine, où au moins l'une des 6 à 8 unités D-glucose constituant la cyclodextrine a été remplacée par une unité représentée par la formule (I) :



(I)

dans laquelle R est un radical représenté par la formule :

1) $-OSO_2R^1$, 2) $-SR^2$,

3) $-NR^3R^4$ (R^3 et R^4 portés par N),

4) $-NHSO_2R^5$

5) $-N(R^7)COR^6$

ou où

R^1 représente le radical mésityle;

R^2 représente un radical alkyle en C_1-C_{20}, un radical alkyle en C_1-C_4 possédant de 1 à 3 substituants choisis parmi les radicaux phényle, phényle à substitution halogénée et phényle a substitution alcoxylique en C_1-C_4, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical dihydroxy-pyrimidinyle, ou un radical purinyle;

l'un des symboles R^3 et R^4 représente un radical alkyle en C_1-C_4, un radical hydroxy-alkyle en C_1-C_4, un radical amino-alkyle en C_1-C_4, un radical cycloalkyle en C_3-C_8, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical alkyle en C_1-C_4 à substitution alcoxy(C_1-C_4), un radical alkyle en C_1-C_4 à substitution phénylique, cependant que l'autre de ces symboles représente un atome d'hydrogène ou un radical alkyle en C_1-C_4, ou bien ces deux symboles peuvent être combinés à leurs extrémités pour former un radical alkylène en C_1-C_4;

R^5 représente un radical alkyle en C_1-C_{20}, un radical phényle possédant un ou plusieurs substituants choisis parmi les halogènes, les radicaux alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, le radical naphtyle, le radical thiényle, un radical isooxazolyle à substitution alkylique en C_1-C_4, ou un radical thiazolyle à substitution alkylique en C_1-C_4;

R^6 représente un radical alkyle en C_1-C_{20}, un radical phényle possédant un ou plusieurs substituants choisis parmi les radicaux hydroxyle, alkyle en C_1-C_4 et alcoxy en C_1-C_4, le radical phényle, un radical alkyle en C_1-C_4 à substitution phénylique, le radical thiényle, ou un radical alkyle en C_1-C_4 à substitution pyrénylcarbonylique, et

R^7 représente un atome d'hydrogène, ou un radical alkyle en C_1-C_4 substitué par un radical alcanoylamino en C_2-C_5, ou un radical benzoylamino,

ou d'un sel de celui-ci,

caractérisé en ce que l'on fait réagir un dérivé de cyclodextrine, dans lequel au moins l'une des 6 à 8 unités D-glucose constituant la cyclodextrine a été remplacée par l'unité ou des unités représentées par la formule (I) avec un agent de sulfonation et on convertit ensuite le produit en un sel, si cela se révèle souhaitable.